Cutting Edge Developments in Post-Infectious IBS, Methane, and SIBO with Dr. Mark Pimentel

Shivan Sarna: Hello everyone. Welcome to SIBO SOS, our very special masterclass and Q&A with Dr. Mark Pimentel. Dr. Pimentel is the executive director of MAST at Cedars Sinai. That stands for Medically Associated Science and Technology. What does that mean, Dr. Pimentel? Hello, good morning.

Dr. Mark Pimentel: Good morning. So glad to be here. What it means is it's a program that I helped start up at Cedar Sinai to develop new technologies for patients. One of the things that I sometimes get a little frustrated with is that pharmaceutical companies develop things in a certain way—not always patient-centered in the sense that, as a doctor, I know what patients need because I see thousands of them and I know exactly the kind of niche of things they need. And so, I felt like maybe we could develop the things for IBS and for IBS that we felt patients were missing.

And so, we help develop those things and try to get them to patients eventually with my lab, with the clinical research, with our whole specialized team. Sixteen people working all for your audience.

Shivan: Wow! We appreciate it. We know it's a labor of love for all of you and a mission. And we're going to be talking about that mission of helping to get everybody cured of post-infectious IBS and SIBO. Go team! Ra!

So, you guys, if you know anybody really rich who wants to contribute to the cause—it's just a suggestion. I'm sure it's non-profit. Anyway, point made.

Dr. Pimentel, I know you have an incredible presentation for us. Guys, Karen and Mariel are in the chat. Let me confirm that I have it turned on—it is. And if you want to pop into the Q&A box with a hello and where you're from, that'd be great.

We aren't taking live questions today because we had so many pre-submitted. And Karen and Mariel are going to help you with customer service.

Okay, go ahead and take it away, Dr. Pimentel.

Dr. Pimentel: Okay! So, I'm going to just share my screen so that you can see what's going on. And here we go!

As Shivan mentioned, I'm here to give you a SIBO update. So some of the stuff you're going to see here is old because I have to give you a background for those who have never heard me speak or never heard the information. Also, there's going to be a lot of new stuff here. Shivan says, "Promise me new stuff." And I promise new stuff. I've got new stuff here—more to give you some really strong and very, very clear insights that we're on the hunt for this. We're close. And I want to leave you with optimism on how we might proceed.

But I know this drives people crazy. Maybe it drives me crazy sometimes. But it's very tricky to separate irritable bowel syndrome and SIBO and to understand how the two of those things blend together.

SIBO affects 40 million people in the US, nearly 1 billion worldwide. So basically, there's a billion people in the world with SIBO. That makes it the most expensive disorder in gastroenterology because of so many people who have this.

And also, think about it, these patients get tremendous testing. I always use this example—and if you've heard me say it, I'm not going to apologize because I want to spread the word about this.

But I had a patient—and this is not unusual, maybe not to this extreme, a 25-year old young woman who, for all intents and purposes, had irritable bowel syndrome. If I would've seen her the first time, I would have made that diagnosis. We would have moved on and started treatment.

But she came to me. And she had all the classic symptoms. I asked her, "So, have you ever had a colonoscopy?" And she said, "Yes, I've had three normal colonoscopies." And that really has stuck with me since then because it's really shameful that a 25-year old person could have had three colonoscopies—which are very invasive procedures, not to mention the possibility of risk. And the first one was normal. Why would anybody do another normal test, another normal test, and then that expense ratchets up?

And some patients have even said they've spent up to $20,000 out of pocket co-pay just in the lead-up to finally feeling like they have a diagnosis.

[05:06] But irritable bowel syndrome, what we're talking about here, you're saying, “Well, what does that have to do with SIBO?” So we’re going to get into that.

Dr. Pimentel: Alright! So IBS and stress. Before we march into that direction, of what is SIBO and how does it fit in with IBS, there's been this notion, and it starts with medicine. Medicine has this ability of saying, “If we don't understand what's going on, let's chalk it up to stress.” We want to help the patient. We want to do the best for the patient. And if medicine hasn't figured it out, maybe it is stress.

And so, for the longest time, IBS was linked to psychological trauma or stress in the history of the patient.

But it's actually been shown that that's not the case. This was a military trial, deployments to Iraq and Afghanistan. And if you shot a gun in combat, shot another human, witnessed human death and suffering, active combat, you’re in combat, those were all studied through the deployment.

Now remember, they were studied before and after deployment. After deployment, they were coming back with IBS essentially—but none of these sort of stressful events.

So, the person sitting at a desk at base camp who didn't have as much stress compared to the active military personnel who would experience

these life-threatening situations, no difference in terms of development of IBS.

The only thing that was different was food poisoning predicted the development of IBS in this population.

So, if you were food poisoned, or you had Salmonella, or Shigella or E. coli or something like that during your deployment, that was what predicted the development of IBS.

And this is really important because this tells us not that stress doesn't cause IBS, but it tells us that even though they had stress, they didn't develop IBS. it's actually the opposite. they didn't get IBS from stress.

Alright! So, what is SIBO? So now, we're sort of flipping, but I'm going to try and put it all in context. SIBO is, if you look at the colon, the colon contains a tremendous amount of stool. The colon, as the arrow indicates, is sort of larger or the large intestine on the outer perimeter of the abdominal cavity. And then, all of the wiggly stuff in the middle is the small intestine.

Remember, there's 15 ft. of small intestine, 3 to 5 ft. of large intestine. So the small intestine really is taking up most of the space.

Half the weight of stool is bacteria. But in the small bowel, there's only 10:3, a very small amount of bacteria. It's like a thousand bacteria for every millimeter. Whereas if you look at 10:12, it's billions and billions of bacteria.

So, how are these things intertwined? I don't know how much the audience knows about *Helicobacter pylori* as a cause of ulcers, but it's a similar scenario. Think of ulcers as—let's say you had a hundred ulcer patients in your clinic H. pylori, that bacteria, probably caused 70 of the 100—70% or 60% to 70%. But the other 30% are caused by other things. Maybe you were taking too much aspirin, or maybe you were taking some medication that was causing ulcers.

So, not all ulcers are caused by H. pylori. But the majority of them are. And that's the cause.

So, the same thing here. IBS is a term we use for a constellation of symptoms. But SIBO accounts for IBS in about 60% or 70%. So, it's almost exactly the same scenario. So, they're intertwined in a sense.

And you'll start to understand this as this is unraveled and revealed to you.

But there are also other conditions that are associated with SIBO. So, you've got to be mindful of this. So, if somebody with SIBO comes in, yes, the majority of them are IBS types of SIBO. But scar tissue or adhesions can cause pseudo-obstruction. It cause it. Narcotics, if you're on morphine or opiates for two weeks, you're going to have SIBO. That's been studied back in the 1990s.

Diabetes or end-stage diabetes, Ehlers Danlos, and all these other things can cause SIBO as well.

But IBS is broken down into three parts. Now we're jumping back and forth, but you'll get this. IBS-C (which is constipation), irritable bowel

syndrome mixed (which is M), and then IBS-D (which is the diarrhea component), the physiology—and again, this will be clear as we progress as well—is that, really, it's two conditions. It's IBS-C, and then the rest of the group because of the antibodies that we're going to talk about later and the autoimmunity linked to the blue circle here, but not as much clearly linked to the constipation or the red on the left.

[10:17] So, this is sort of the spoiler slide. But it's really sort of meant as a template of what I'm going to describe to you. And that is we start now, we know food poisoning is the cause of IBS in a large proportion of cases. And that this toxin, cdtB and the autoimmunity that we're going to talk about leads to changes in the nerve function of the gut. It leads to bacterial build-up. It leads to IBS. You could call that post-infectious IBS (which is another terminology you will read about or see on the Internet). But in essence, post-infectious IBS is IBS. It's just if you can secure that is from food poisoning, you can give it that nomenclature or that name.

Dr. Pimentel: We're going to focus on the right first briefly. A lot of these things, we've talked about before, but we have some additional pieces of information that I want to share with you.

This is an old meta analysis that I've shown many times. It basically illustrates that if you're IBS, your chance of having a positive breath test is much higher than if you're healthy.

So, the single center line that goes all the way down to the number one at the bottom, anything to the right of that means that the study was statistically significant, and that the odds ratio of you having an abnormal breath test if you have IBS is 9.6 times higher chance that your breath test is positive—which is a huge number, and very, very prominent.

So, that's what we were seeing, that the breath tests were positive. But people were arguing, "Well, the breath test, maybe sugar is getting into the colon, or maybe the transit is fast, maybe it's not bacterial overgrowth, maybe it's something else." But I can tell you, for a number of reasons, this is all going to become clear this year.

But breath testing is the staple of what we do and how we diagnose bacterial overgrowth in IBS or in any other condition. And so this is what breath testing looks like.

So, this is the human digestive tract. And the lungs are included there because that's where the breath comes out. But basically, you ingest or drink a syrup containing a sugar. And if you drink a sugar that's not absorbed, it will go through and through and through the gut until it reaches bacteria. And then, when it reaches bacteria, they will produce gases. They will produce hydrogen, carbon dioxide, methane, and an additional gas which is sort of the new thing we'll talk about later. But those three gases are what are measured on the current breath test.

Carbon dioxide, humans produce. So we can't use that as a marker of bacteria because we don't know if the CO^2 is coming from humans or from

bacteria. So we measure hydrogen and methane because humans don't produce that.

And so, those go to the lungs. Number three shows up in the lungs, and then out the breath. And we measure the exhaled air for the concentrations of those gases.

But as I mentioned, there is a fourth gas. But really, it's a third gas because carbon dioxide doesn't separate humans from bacteria. So there's three gases that tell you about bacteria.

But it's a very tricky relationship because hydrogen-producing bacteria, when we talk about the breath test, we used to say hydrogen breath test. We don't say that anymore. We say lactulose breath test or glucose breakfast because hydrogen is not the only gas and may not even be as important as you'll see later.

But hydrogen-producing bacteria are the fuel for two other groups of organisms—the methane producers—which are not even bacteria, they're archaea. And they produce methane. But look at the numbers. So you take four hydrogens to produce one methane. So that one bug needs four of those molecules of hydrogen to make one molecule of methane.

So, it's a sink. It's basically siphoning off a lot of hydrogen to make that methane.

Hydrogen sulfide producers are the other category. We couldn't, up until recently, measure hydrogen sulfide in the breath. But hydrogen sulfide-producers, five hydrogens just to make one hydrogen sulfide.

Alright! So, we'll get back to hydrogen sulfide in a moment. But let's continue on the path of diagnosing overgrowth in IBS because we're trying to make the case that IBS, 60% to 70% of IBS, is overgrowth. And if you look at this graph, this is from a Swedish study from all the way back in 2007 showing that if you use different cut-off's of bacteria, and you can see the right cut-off greater than 5000 bacteria per milliliter. And you can see 43% of IBS patients have that number and that they have this so-called overgrowth using 5000 as a cut-off.

But if you use 1000 as a cut-off which is really the normal range 60% In this study, 60% of IBS patients were positive. Twenty-seven percent, these are not healthy people, these are people with illness getting a scope—and 27%. And so it was highly statistically significant. Some of those patients may have had overgrowth for other reasons because they were ill. They weren't healthy controls.

[15:09] Now, we now are starting to unravel what bugs are part of SIBO. And what I can't tell you today, sorry, is that we are presenting a major podium session at the big GI meeting in June—so I can't talk about it because it hasn't happened yet—where we describe all the bugs that are part of SIBO in a very large study, which I'll show you sort of the nuts and bolts of how this study is done during this lecture. But in this trial from Pyleria, E. coli is a big player, Klebsiella is a big player in SIBO.

Dr. Pimentel: Now, it doesn't look much different, those bugs. But remember, the y-axis is a log 10 access. So when you go from one to two, it's ten times higher—2 to 3 is ten times higher than two.a So that's a hundred times higher than one. So, for every incremental rise, it's 10 times more bacteria of that type. So Klebsiella and E. coli are markedly increased.

I've shown this before. And it's kind of a messy thing. We have much more glamorous graphs now coming with the new technologies and the new software. But these are sort of a pie chart of what's going on in the small bowel in humans who are normal. A lot of little pies, a lot of different bacteria. But a lot of good balance.

In IBS, the balance is thrown off a lot. A lot of Aeromonas , a lot of E. coli and Klebsiella—which we talked about. But again, we'll have much more granularity on that.

So, the MAST program, one of the flagship if you want to call studies in the MAST program—this took a long time to get up and running—is the *ReImagine Study*. And this is what we're presenting, the first few abstracts of, in a very dramatic way at the DDW meeting.

The ReImagine study, we feel that the small bowel microbiome, first of all, has not been captured. So we are the only center in the world doing a large scale small bowel microbiome assessment using the modern techniques of deep sequencing, culture and the like.

We think the diseases that are related really to the 15 ft. long small bowel where you absorb food and nutrients and so forth—that's where things get

absorbed. So if you have chemicals that are harmful to you from bacteria, it's going to be absorbed from the small bowel because it's an absorbing surface.

So, obesity, small intestinal bacterial overgrowth, scleroderma, neuromuscular disease, autoimmune disease, even the effects of medications, we're studying hormone metabolism, all of that is part of the ReImagine trial where we hope to get up to 10,000 people. But we have a lot in already and a lot of data already. And we're super excited about presenting that.

But this is the kind of stuff we're collecting. We're collecting hormonal analysis—histamines, serotonin, autoimmune markers, immune markers. We're looking at culturing plus the deep sequencing, plus all the genetics of the human.

So, this is a very, very ambitious project that is already bearing fruit. And I wish I could tell you more because the amount of excitement we have about this project and our results already is really amazing. So hopefully you'll hear more as time goes by.

But I want to give you one teaser. If you think about this large intestine, half the weight of stool is bacteria. But half of the bacteria that you find there are dead. They're not even producing anything. But you can still amplify the DNA. So it makes it very difficult to determine what bacteria are important to disease when everything you're measuring, most of what you're measuring, is dead.

The small intestine is different. What we measure are live bacteria. And we've actually proven that with comparing to culture and other techniques to show that they're alive because there's a lot of nutrients in that environment and other factors.

But this is what the large intestine on the left looks like, and the small intestine on the right. So one of the—it's not a pet peeve, but it's more of a point of clarification. The Human Microbiome Project—maybe you've heard of this—the Human Microbiome Project was a project that was started in the 2000s, but in 2007, a major paper was published saying, "Okay, ta-dah, here's the human microbiome," and they used stool as a surrogate of the gut. But as you can see, the graph on the right looks completely different than the graph on the left. And the bacterial composition of the small intestine is completely different than stool.

So, you cannot say what's in the stool represents what's in the 15 ft. of small bowel, the longest segment of the gut. And we're going to illustrate that in real specific and very, very tangible detail in DDW to describe all the organisms of the small bowel and why they're so important and so uniquely different.

But one of the things we found way back, shifting gears now to methane, is—this is a paper from 2011. It's still a little old, but it's still relevant today. If we were to repeat this study with all the new data we have, this would be even more impactful and powerful because we now know methane and constipation go together.

We also know that if we put methane into the gut—and this was an animal trial. If you put methane into the gut, you get 70% slowing of transit. So, methane slows the gut down.

[20:09] Now, it does it in a very unique way. It doesn't paralyze the gut. It actually causes the gut to contract in a way that's not peristaltic, sort of holding things back. And that can be part of the reason why people get cramps because it actually causes sort of a spasticity of the gut.

Dr. Pimentel: But the point is that methane slows the gut. And as a result of that, we could actually predict people with constipation just by measuring methane.

But I kind of don't like this study. This is a study that we did, but I don't like it because it suggests that we're using nothing to diagnose constipation. I don't want to use methane to diagnose constipation. If a patient is constipated, and they have methane, the methane is not telling me they're constipated. It's telling me how to treat them because treating methane is different than treating hydrogen. And we'll talk about that briefly.

I've already showed you this just to refresh your memory. But what I wanted to get to is the third gas before we get into treatment.

So, we developed a device now—and this doesn't look very exciting. It's a box with a computer on it because it was the first prototype. So now the new device is coming. But it’s the first prototype of measuring hydrogen, methane and hydrogen sulfide all at once. And we actually validated this instrument and this technique at the last meeting at DDW.

Basically, I'm going to show you one slide to show you that hydrogen sulfide equals diarrhea.

So, if you go back to this slide, going back once, now we know hydrogen really doesn't predict any. It may predict response to drugs (which I'll show you later), but it doesn't predict symptoms.

So, for example, we were always struggling with, well, if hydrogen is 100 on the breath test in one patient, and 50 on the breath test, that's half on the other patient, why do they have exactly the same bloating, the same intensity of diarrhea, and you couldn't predict symptoms with it, whereas with methane, the more methane you produce, the more constipated you were? Because hydrogen is just the fuel for the two gases that we think determine symptoms.

Hydrogen sulfide is very toxic to the epithelium, to the lining of the intestine. So hydrogen sulfide, the higher it is, the more diarrhea.

So, going back to this slide I just showed you, for every 1 ppm—one part per million—rise in hydrogen sulfide, we saw 15 point higher severity of diarrhea. So it's proportional. So this acts like methane, but on the opposite side of the equation.

So, let's talk about treatment. And then we're going to get into this whole post-infectious IBS and autoimmunity because that's really the most interesting and new stuff.

But this is the Rifaximin trials. Rifaximin has become the staple treatment or irritable bowel syndrome. It's FDA-approved for IBS. It's off-label for

SIBO. But it's kind of confusing because SIBO is IBS because we believe that it's mechanistically related. But your treatment is for irritable bowel syndrome because that's how the patients were enrolled and defined for the trial.

But essentially, Rifaximin, in this study, you take it for two weeks. And you got four weeks in the follow-up periods. So two weeks of treatment, four weeks of follow-up right after that. And everything to the right of that center line again that goes down to one, means that it was statistically significant. And everything was statistically significant—whether it was pain, the global symptoms, the new very challenging FDA endpoint and so forth. But even the next slide, three months later, almost everything was still statistically significant.

So, for the first time, there was a drug that did something to IBS patients—you could say *permanently* (permanently meaning you weren't on the drug, and you were still getting the effect of the drug many, many, many weeks later).

And so, the point is it must have impacted a causative factor in IBS. And we believe that causative factor is the microbiome and SIBO at least in my opinion.

So now, what's amazing about Rifaximin is we've studied this now—and this is published. This is in Digestive Diseases and Sciences now. It's no longer an ACG meeting. But what's amazing about it is, over a

decade—now, it's been off-label use. And then of course, it got approved in 2015. So it was used for IBS off-label.

But there's been a 30% reduction in patients coming into my office, coming to even GI offices now over this period of time because patients are using it at lower levels of care now—which saves money, saves the headache for the patient (it means that patients are running around less). And so Rifaximin has made a dent in IBS for the first time like no other.

And there's a 2.5% increase in Rifaximin use over that same period of time.

[25:21] So, I was going to tell you that even though I've sort of said hydrogen is a fuel, it is a predictor. So in this study, which was presented at ACG—and there's now papers developed (they're going to be submitted for publication in the coming days or weeks), basically, if you look at the Rifaximin study, 44% of people respond to Rifaximin. That's the first bar. But if your breath test was negative in the study, only 25% responded.

Dr. Pimentel: So yeah, you still can respond. But only a quarter of people can respond if the breath test is negative for hydrogen. But if the breath test was positive, 56% responded. So that was much higher.

If the breath test was positive, and Rifaximin made it negative, 76% of people met the FDA endpoint—which was a tricky endpoint.

And so, this is very meaningful, meaning that the breath test was detecting a surrogate marker.

Okay. So this is now treating methane. Look at the middle bar because it's the Rifaximin bar. We made a big deal about Rifaximin on the previous page. But Rifaximin doesn't work for methane. Neomycin, you could argue on the red bars, maybe it works slightly better than Rifaximin even though that's an older product.

But what we knew from studying the methane-producing organisms in test tubes is that if you combine Rifaximin and neomycin together, you got a much better eradication of the bug. And we don't understand why because when we developed antibiotics, antibiotics were designed for bacteria. They weren't designed for fungi, for example. They weren't designed for archaea. Archaea are methanogens. So, on the right bar is a methanogen, and yet it's responding to antibiotics. So that means there must be some way that it's affecting them.

Anyway, look at the yellow bar. The clinical response created an 80% improvement in constipation, meeting the constipation result point. And so this was a really robust effect.

However, the problem with giving Rifaximin and neomycin, I'll show you in the coming slides.

We then did a double blind study where we took real drug neomycin alone with placebo and compared it to neomycin + Rifaximin. And you can see that neomycin and Rifaximin, superior in this double blind study in treating constipation. Bloating also got better.

But this is the point. The point is it's not about the antibiotics. It's about getting the methane less than three. When we got the methane less than three, that's the patient who did best.

And the problem with the response that I showed you here with bloating and with constipation is they tended to last about a month on average. So it's not like the Rifaximin story for IBS-D where—and I've had patients in my clinic where I treat them, I don't see them for two years, they're still better. And then, maybe they relapse two and a half years later. Some people, of course, relapse at one month or two months. But we can have patients who relapse very late.

With methane, it's a little different. It relapses more easily, meaning it's a more sooner relapse. But it could be the nature of the organism. It could be that these are antibiotics designed for bacteria and not from methanogens. So we had to come up with something better.

So SYN-010, I know a lot of the audience has heard about this because I get a ton of emails and comments, "When is this coming?" So let me tell you the story and tell you when it's coming.

But its lovastatin. Now, lovastatin is produced by this fungus on the screen which is Aspergillus. And the little vesicles produce this lovastatin. And the lovastatin is produced not for human cholesterol, but in fact, for the environment in which this fungus lives. And it inhibits methane. And that's what lovastatin does.

And in this first study we did where we took this lovastatin—

Now, by the way, people say, “Well, what about Crestor”—excuse me for using trade names, but some of atorvastatin and other statins, “could it work?” It turns out that every time a human has tampered with the molecule lovastatin in order to make it better for human cholesterol, it has destroyed what nature created to inhibit methane. So, you can't use the more modern ones.

Plus, the lovastatin is designed to be absorbed for cholesterol. So, this product here is a delivery system for lovastatin that makes sure it doesn't get absorbed. So there's literally very little that gets into your bloodstream, so your cholesterol would not be impacted.

Back to the story…

So, if you look here, the methane—or sorry, I'll show you the methane in a second. But the red bar or dots are the use of laxatives as rescue. And what you can see is that the patients on the highest dose are using far less laxatives than the green bar or green dots where they're using placebo. They need a lot of laxatives because their constipation is bad.

[30:09] And on that basis, we've started the phase two trial. It's 150 patients, only Cedar Sinai—I'm sorry if you're in other parts of the country—people less than 65 years old, have bad constipation. And it's a three-month trial.

Dr. Pimentel: The good news is it's not a placebo drug trial. It's a placebo drug drug trial. So there's three arms which means there's a 67% chance you get real drug as opposed to placebo. Some studies, it’s 50/50. I know people are always

worried they're going to get in a trial and get placebo. At least the odds are higher.

But we're really excited. This has launched. We have a huge lineup of people for this trial because it's very exciting and a lot of people are still suffering with this condition and their methane.

Alright! So now, we're going to work on the left side of the screen in the last sort of half of the talk. Acute gastroenteritis leaking can be caused by E. coli, Campylobacter, Shigella, Salmonella. These are names you've probably heard when you hear about an outbreak in a particular restaurant. And so, those things can lead to IBS ultimately or overgrowth. And there's a toxin that they all produce commonly. And interestingly, this is really one of the only toxins they all produce commonly. We had to find something in common with those organisms and why any of them can portend the development of SIBO.

So, what I'm going to do is focus on this side of the screen now.

Now, I don't know if there's any doctors on the call listening in. But as a clinician, as a doctor, in 2019—this is a study from 2017, but now I'm saying two years later after this trial. There's a doctor that doesn't know about post-infectious IBS. And that IBS is post-infectious in the majority of cases. It's a concern because this trial from the Mayo Clinic looked at 45 outbreaks, the published studies of 45 outbreaks in the world, and showed without a doubt definitively that if you get food poisoning, you have an 11% chance—11% of people who were exposed to food

poisoning go on to develop IBS because of seeing that infection. Full stop, food poisoning causes IBS.

So, it's really important to know this because let's think about inflammatory bowel disease, Crohn's disease, ulcerative colitis, we still—all the money from the NIH and all the money out there for IBD, speaking of (there's no money from NIH for IBS), despite that, we know more about the development of IBS now because of this, because of knowing food poisoning is the starting point. We now know more about the development of IBS than we do Crohn's or ulcerative colitis.

So, that's a very meaningful change in this condition. And the people who don't know about this, in terms of medical practitioners, really need to pay attention to this new area.

It turns out there are risk factors, but it's all about that first bullet—the severity of the food poisoning, the severity of the—well, I actually put it all in caps because if you have blood in the stool, if you needed antibiotics, if you had fever, you had to be admitted to the hospital, all of those things mean it's not 11% for you, maybe it's 20% for you, the chance of developing IBS. The sicker you were, the more likely you are to develop IBS from it.

Psychological factors play a role. But I want to focus, really, women are more likely to develop IBS from food poisoning. So if you took a hundred men and a hundred women, food poisoning, the women are more likely—almost every trial, women are more likely to get IBS from that.

So, how does that happen? And I will try to address that a little bit as we move to the final slides.

But this is an interesting study because we said, "Well, how much of IBS do we think could have been food poisoning?" This was a model where we took 300 million people, the approximate population of the US, and we said, "Okay, let's bring 300 people into the US right today, nobody has IBS, zero.: And looking at the Center for Disease Control's rates of food poisoning in the population, and then created a model, we found that after about 12 years, 9% of the entire 300 million would now have IBS based on everything we knew at the time.

And so, this suggests—remember, IBS is about 12% to 15% of the population. This suggests that at least 60% to 70% of the IBS population could have been derived from food poisoning.

Again, these are the evidence for suggesting that 60% to 70% of IBS is SIBO, 60% to 70% is food poisoning-related, based on data like this.

I've showed these slides before. But they become more and more meaningful with time as we start to unravel the autoimmune part of this.

[35:05] So, we wanted to show what happens. Could we create rats with IBS? So rats on the left, they've got no Campylobacter; rats on the right got Campylobacter infection. They recovered.

Dr. Pimentel: And then, three months after that, meaning three months of no Campy, no more Campy in the stool, and they just sit around, we were then able to look at their stool consistency and see if they had like weird bowel

function, and then see if they had bacterial overgrowth by QPCR (which is a really sophisticated technique, at least at the time, to see and quantitate bacteria).

And what we found was 27%—we'll focus on the right—27% of the rats who saw Campylobacter now have SIBO. But that SIBO, looking at the pink bar, if they had Campylobacter and SIBO, 80%+ of them had weird bowel function.

So, we had, for the first time, a model of animals that had bacterial overgrowth, post-infectious IBS all wrapped up into one.

Why is this important? It's important because in 2008 to now, we've been able to study this model to figure out the steps and the nuts and bolts of why this is happening. And when you understand why this is happening, you understand how to treat it ultimately in the end. And that's what we're doing.

So, back to the toxins. So we know Shigella, Salmonella, Campylobacter, even C. difficile—for those of you who've had a C. diff in the past—can cause IBS, but also share this one toxin, cytolethal distending toxin. And this toxin is a culprit here—but it isn't what we thought. So let's walk through the studies.

On the left, rats got the regular Campy that causes the IBS. In the middle, the rats got a Campylobacter that was missing the toxin. We deleted the toxin from the bug. So it shouldn't produce CDTB. On the right is mimicking you going to a food truck that you know has Campylobacter,

and you're taking Rifaximin the day before, the day of the Campy, and the day after. So you're trying to prevent the Campy from making you have IBS.

And sure enough, the rats who got Rifaximin, they had the best stool consistency—one is normal. The rats with CDTB in them got the most. And the rats without CDTB were mitigated. The point is CDTB was implicated.

So for the first time, we said, "Okay, we have a factor in the bacteria that we think is causing this." So we then took tissue—and this is hard to explain, it's a lot of science. But look on the left, this is just rabbit antibodies. They don't find anything. It's all blank. We put rabbit antibodies on the left, but it's all clean, no brown staining.

On the right, we developed rabbits who had antibodies to CDTB. And they took that CDTB antibody, put it on there. And the nerves of the gut all light up. So you can see the ganglia are pointed out. And the DMP-ICC is a very complicated name, but those cells are what make the migrating motor complex, or the cleaning wave of the small intestine, and it's that wave that, when missing, causes bacterial overgrowth. So those cells are pacemaker cells for that wave, which I will show you right here.

This wave is super important to clean up during fasting, during the nighttime When you're not eating, and you hear a gurgling sound in your stomach, it's cleaning. It's cleaning up like a dishwasher would clean your

dishes at the end of the day. And then the small bowels beautifully clean for the morning when you start breakfast.

If you're missing those brown, little cells, DMP-ICC's, or they're reduced, this doesn't happen often enough. And then, you can get overgrowth This is part of the mechanism. But it turns out—going back to this slide—that the antibodies to CDTB caused this brown staining even in the rats who never saw a Campylobacter. So we now knew that it's something in these antibodies (or reacting to the CDTB) was causing you to react to you and the nerves that are you.

And so, we knew that it was some—what we call *molecular mimicry*. The toxin was looking like something that is you, creating an antibody to you. And as a result, autoimmune disease.

So, we wanted to prove that in this. So we said, "Well, let's take the Campylobacter. Let's suck out the CDTB and purify it. So now, we're going to give to the rats, like a vaccine in the arm,in their back leg, we put CDTB only—no Campy, no infection, no food/drug, no nothing—and then see what happens to them.

[40:03] Well, they develop antibodies to CDTB like crazy because we've put CDTB in. But they also developed antibodies to themselves, the anti-vinculin antibodies that we'll talk about here in a moment. So, what is vinculin? We're going to talk about that.

Dr. Pimentel: But one more thing because this is probably the more important thing. These rats, just from getting CDTB injected into them, the level of the

anti-CDTB antibody predicted the development of increased numbers of bacteria in the gut—duodenum and ileum—and a decreased expression of vinculin and a change in the stool wet rate.

So basically, we were creating IBS just with seeing this toxin.

So, what is vinculin? These are cells in a very beautifully depicted fluorescent staining from our lab. But if you look at the red arrows, they're pointing to these tufts. I don't know if you can see my arrow. If you can't, I'm sorry. But there's little, red tufts at the end. And that's vinculin. And the green are the filaments or the skeleton of the cell.

So, you can see that these red areas are reaching out to grab onto the next cell, so that the nerves and the wires of the nerves are connected to each other.

This is another depiction. This is actin. This is the green in the previous slide. And this is vinculin over here. It's part of like a motor that makes the cell move along the actin to create these sort of little tendrils or fingers out to grab on to the next cell.

So, what we were seeing in humans was you get CDTB, you get food poisoning, you form antibodies to this CDTB. And you form [them] because you don't know it. It's like a foreign chemical. So you're reacting to it.

But one of these areas has a similarity to vinculin, and you develop this vinculin antibody.

So, we developed a test to measure anti-vinculin and anti-CDTB in humans. And could it diagnose IBS specifically as caused by food poisoning? And we compared it to Crohn's, ulcerative colitis, and Celiac as well as healthy controls.

But in the end, the test worked like this. So you, in a GI office (or modeling a GI office), there's a 56% chance before you even see the patient that it could be IBS because it's so common. And if one test was positive, or two tests were positive, you have a 95% chance that it's IBS. So it was very diagnostic, very—what we call *post-test probability* was very high. If both tests were negative, it drops to 24%.

But the sensitivity and specificity of the test needed improvement. So we've actually launched a new test that is second generation because there were some issues that we detected along the way that we could improve to make the epitopes more exposed in the dishes. So we could actually see the intensity of attachment much, much better.

So now, the specificity for both markers is more than 90%. And now we get to 98% certain. And this will save a ton of money because imagine that patient, that 25-year old woman I mentioned at the beginning, if she simply had a test, it was positive, you don't need colonoscopies—because the certainty is 98%, the specificity for either marker alone is 90%. So it stops the unnecessary testing.

This is an animal study just taking it a step further. This is new data. Shivan says, "New data, new data, new data…" So we injected these antibodies into these animals—and they're alive. And then, we were able

to see that the antibodies go to the gut. And the gut has these antibodies on the right. And you can see the antibodies are right in the gut and the small intestines at the top. It's as though it's attacking—if you want to say it that way. But we can see the antibodies glowing in that section just from injecting it in the blood.

These are some clinical of observations we've made. They're not published yet, but more interesting things. Higher anti-vinculin antibodies means greater bloating and distension. We see some of the worst bloaters have the highest levels of vinculin, and also makes *we think* your SIBO more difficult to treat. So, some of the patients who've taken antibiotics, doesn't work, doesn't work, doesn't work, we're seeing that these antibodies are super high.

I know that doesn't help some of you in the sense that "Well, what do I do? How do I still get rid of the overgrowth if I have these high antibody?" But at least, for the moment, it explains why you're tougher than somebody else.

These antibodies also work in mixed. So they work in D, in mix, but not as much in C-IBS. And this was published about a year and a half ago.

[45:13] So, I want to show you a new thing again. It's something I haven't shown on a slide. And this is a patient, so just to show you how these antibodies work. He got gastroenteritis. He was traveling to Mexico. And then, after the gastroenteritis, he ended up in the hospital here in the US just coming back from the trip, and now had severe bloating and IBS.

Dr. Pimentel: And this was how the CDTB response and anti-vinculin response work. And it doesn't show up, that's so weird. Okay! So, I'm going to describe it.

So initially, the anti-CDTB goes way up, and then drifts down over time, over months. The anti-vinculin comes in later. So about two or three months later, the anti-vinculin antibody starts to rise and stays up. Remember, once the CDTB is gone, the infection is gone, you don't have any more CDTB around. So the CDTB antibody starts to drift down.

With the vinculin though, you have it in your body, and so you can continue to form it which makes the autoimmunity more potent, keeping you impaired. And Shivan, I'm sorry. This one doesn't—if the graph don't come in, I can send you that slide if you want to share it with your audience.

Okay. So really complicated. I think you're going to see the decks. So you can like read through this very slowly. But this is how we think it works. If both antibodies are negative, we don't think food poisoning was the cause of the IBS—or SIBO for you. If anti-vinculin is high, and vinculin is low, it diagnosis IBS. It may mean the infection was recent, or that you don't have a tendency to form as much autoimmunity. If the CDTB is low, and the vinculin is high, it could have been that the infection was a long time ago, but you still have this antibody that's hurting you. If both are high, it could be recent infections coming and going. And I'll show you why that's important.

And so, this is just starting to explain how the two antibodies work in tandem. But if their vinculin is very high—and we've seen this in the pseudo-obstruction patients—we think it portends a neuropathy.

If you go back to the rat study way back, the higher the antibodies work, the sicker or more overgrowth the rats had and the less the vinculin was. So we think that it's actually more damage with higher titers of these antibodies.

I'm going to show you something just because. But you're not going to do this. Promise, you're not going to do this because I know there are people out there willing to do anything for their overgrowth. But I want to show you this. This is a case series. This is not a published study. We're kind of reluctant to publish this only because it's a small number, but it tells me an important fact. So these are people that we put in here that are extraordinarily bloated. And I don't want you to go out and do this.

But they were so severe, they were in and out of the hospital. They had very high anti-vinculin antibodies. And we then filtered those antibodies out almost like dialysis or plasma freezes.

With the filtering of those antibodies, of course, the antibodies were gone. But the patient felt the best she had in years—no bloating, no dissension. Her bowel movements became completely normal.

But a month later, two months later, the antibodies come back because we haven't gotten rid of the cells that produce the antibody. And of course, they're re-bringing the antibodies back into the bloodstream.

My point is we know that the vinculin is critical, and that if we can get rid of it, we think we can make a huge impact on patients.

And so, the reason for this slide is to tell you we're hot on this. We want to fix this. But plasma freezes is not the answer because it filters all antibodies. It makes you immunodeficient. So you don't want to do this at home. It's a proof that this is a potential mechanism for understanding vinculin as a cause.

So, patients perspective: “Finally, I know what I have.” I hear this all the time. That's why we like doing this testing—less testing. Once the test is positive, you don't need to do anything more. You’re diagnosed in a handful of days. Sooner diagnosis means less cost because if you're not running around doctor to doctor, getting test after test after test, you're going to save money for yourself, for your health, for the healthcare system—and the frustration as well.

So, the patients know it’s food poisoning. So now you know why you have what you have. And it's not in your head, it’s an organic marker. So I’m going to skip #5 because this is super important for the last few slides of my deck. And you can potentially follow people in time.

[50:05] We already showed a time study. The slide didn't work properly which I'll send to Shivan. But over time, if the antibodies can be brought down, or they go down, we think that's a good sign. So if a year from now, the vinculin comes down further, you know you're heading in the right direction. And eventually, maybe your IBS goes away if you never get

food poisoning again. And we think this is the template for future therapies.

Dr. Pimentel: So, back to this (because I have one last teaser for you). And that is IBS, is it because of all this damage or risk for food poisoning?

So, did Campylobacter give you this toxin, make you have this autoimmunity so that every time you're exposed to food that's slightly off, you're more likely to get food poisoning than somebody without IBS? And the answer is yes.

So, let's talk about Campylobacter just briefly. It's a major scourge. It's one of the leading causes of death in children under the age of two. And I'll speak to that momentarily.

But this is the study. I spoke to my colleagues in the military, and I said, "Well, what if you already have IBS, and then you get deployed? Do you have a higher chance of food poisoning?"

You're basically already damaged. Does that mean you're going to get sick easier than somebody else if you have food that's not right?

So, IBS patient, going to deployment, 2.9 times higher. So yes, you have IBS, you're more likely to get sick when you travel.

You're also more likely to jack those antibodies higher, which means it's harder for the doctors to treat you if you get food poisoning again. And we've seen antibodies jump up with people who get food poisoning a second time.

One last thing, and then I'm done. And we'll go to questions. So, obviously, the world is different in different parts. Underdeveloped areas have tremendous difficulties with sanitation, clean water, and the exposure to these pathogens.

I'm going to tease you with some information. But we're working with a group that's working in Tanzania with the Gates Foundation. And these people in these environments where the poverty is so terrible that they don't get clean drinking water, they get acute gastroenteritis. And the children here—imagine Campylobacter. Most people in the western world don't see Campylobacter. These children under the age of one—in fact, the statistic is that by age six months to a year, 60% of the children in these areas have seen Campylobacter or have been infected with Campylobacter.

And they get an autoimmune enteropathy essentially. That's what we think. So, this dissension that this young boy has who's been exposed to this malnutrition may not be all that it appears because their bowels actually distended, almost like a pseudo-obstruction.

And in the underdeveloped countries, it is called *bacterial overgrowth* (which is related to what we call *tropical sprue)*, chronic distention, vitamin deficiencies. Some of them even die from the malnutrition.

But they are also the spreader of the infection because if they're the one that keeps getting infected because the way their gut functions, they're

harnessing or harboring these pathogens because of what the bug did to them. So it actually keeps the bug in the population.

We can't fix this. This is a political problem. Maybe we can fix these things. And I'll speak to that just briefly, maybe immunize.

So, this is one of the things that I want to show you. We've looked at the vinculin antibody. And in malnutrition, the vinculin antibodies are through the roof. So these young children who are quite malnourished, exposed to pathogens, we think it's really important in the underdeveloped country as well.

And so, it's just an extension of the most extreme examples of what these organisms can do to people.

But what we're trying to figure out is how do we get a vaccine developed that we can prevent the autoimmunity and protect against getting CDTB. And we have really good signals on where that is, and we're getting at it.

So, in summary, the diagnostic part, wrong criteria, which is the diagnostic tests for IBS, which is just clinical criteria. They really aren't very good, but easy and available. But they really don't tell you about pathophysiology. There used to be some genetic testing, which wasn't very helpful.

Fecal calprotectin can be helpful, but really, if you're positive, you have inflammation. Maybe you have Crohn's. But if you're negative, it doesn't tell you you have IBS.

The breath test is helpful. Specificity is somewhat low, but you'll see some data at the DDW that maybe speaks to that. But the blood test, easy to get. It's available. High specificity. It makes IBS a diagnosis of inclusion. You now have it. It's based on the pathophysiology—which I've convinced you of hopefully. It tells you therapy because it's going to tell us how we're going to end up treating these patients, and it reduces costs.

[55:13] So, my final slide is, most of IBS appears related to SIBO. Vinculin is an adhesion complex protein that appears to be super important in this whole process because antibodies to vinculin can damage the nerves of the gut. And that's gaining in importance.

Dr. Pimentel: Hydrogen sulfide is going to be key to understanding the diarrhea and perhaps guiding treatment until we figure out how to get rid of vinculin.

And methane is associated with constipation. And we're very optimistic that SYN-010 is going to be the microbiome-based approach to treat methane.

And so, just to show you this in outline, remember, everything we're doing is very systematic. I've showed you this picture. But we're developing a vaccine here. We're developing the blood tests, which I've showed you here, for developing preventive therapy. So those are prokinetics. That's why we use prokinetics, because we want to improve the neuropathy—the neuropathy is there, but some of the wires are connected, and we make them work better.

We're developing new breath tests, hydrogen sulfide breath test, and new therapies. Of course, Rifaximin is one of them. But the future may have others. And I already know of others that were in the works.

And this is our team working for you all out there. And they don't always smile this broadly because we work them very hard. But they're very cohesive team. They enjoy working with each other. And I certainly enjoy them as well.

[56:39] And that's the talk folks.

Shivan: Oh, thank you so much. Thank you so much.

Dr. Pimentel: How did I do for time?

Shivan: You did great. You did absolutely brilliantly. Thank you so much.

[QUESTION AND ANSWER SESSION BEGINS HERE]

Shivan Sarna: I think it's a huge, huge, *huge* development here guys. It is so powerful. And I'm totally thrilled and humbled to be able to help facilitate getting this information out.

I know you guys are working like 24/7, Dr Pimentel. So please send your team our love and gratitude… big time!

Okay. So, a couple of questions that I know are in this huge list.

So, what's the name of the test? And how can we get it? So, let's just talk about IBS Smart Test for a few minutes.

Dr. Mark Pimentel: Sure! So, I helped found the company. I'll give you that as a disclosure because I wanted to guide the science. I wanted to make sure that this was patient-centered and not company-centered.

So, I've done things differently this time. But more importantly, it's a second generation test. And it's more specific. We figured out some of the quirks of the test. And again, it's 80% to 90%. But it's IBS Smart and it's at www.IBSSmart.com. You can order the test that way.

But your doctor really has to order the test because we want to make sure that the doctor—you know, that is covered by your insurance for the most part, so that you don't have to pay for it because that's covered.

Shivan: And even if your insurance doesn't pay for it, it's not overly expensive if you do need to do cash. And I think there's a link there on the IBS Smart Test website where either the lab will reach out to your doctor and solicit that prescription. So it's very organized, very professional. I want you guys to be aware of that. I mean they have their act together… big time. They're great.

Dr. Pimentel: Yeah. Basically, it's all of that. There is a portal for the doctor to order kits. They have to draw the blood in their office. And then, there's a portal for patients to say, "Well, how can I get it? And how can my doctors…" Or you can tell us your name of your doctor, and we'll reach out. The team will reach out.

But the point is we're trying to stop the ridiculous expenses and things that patients go through. That always irritate me. I think patients are just getting over-tested honestly.

Shivan: Markel is saying fabulous cutting-edge information. It's helped clarify some questions that she's had some with some of her difficult patients. Fantastic!

When is SYN—is it SYN 0-1-0 or SYN-010? When is that going to be available?

Dr. Pimentel: The trial is on now. Things are finally moving. We were in the quick sand for a long time, but I think we're getting to the right place. I'm very excited. I know the patients are super excited to get in.

We still have a lot of room in the trial. So anybody who lives in the LA area, and you're methane, please share this information. We're happy to recruit more patients. We have to get to 150 very quickly in a few months. So we're getting there.

Shivan: Okay. So, how would they reach out to you guys in order to participate or be a candidate for participation?

Dr. Pimentel: They could—oh, gosh! I have to get the MAST email. I'll have somebody pull that from the other room and just pass a message to me, so that I can give it to you later.

Shivan: Okay. And then, the other question is they take the IBS Smart Test, they get results, they show that they're positive, is it more likely that they're methane or that their hydrogen?

Dr. Pimentel: Yeah. So this has confused a lot of people. But let me sort of—I use it all the time in my clinic. And I could explain how I use it.

So, it's sort of like you have a heart condition. You're having a heart attack. You have an EKG. And the EKG says you're having a heart attack. And then, you do an ultrasound of the heart to look at the function of the heart to get more definition of what you're going to do.

So, maybe you have a heart failure, and you have to use these medications. The EKG doesn't tell you to use heart failure meds. It only tells you that you are having a heart attack or there's heart dysfunction.

So, it's the same thing here. But the test, the blood test, tells you you had food poisoning. Let me give you the best example possible. So I had a patient who was positive on the blood test, treated with rifaximin for her IBS. She's amazing. She feels terrific. She says, "I'm going to Costa Rica. What should I do?" And I said, "Well, you've got to do something."

[05:11] So, she goes to Costa Rica, but I give her—and this is off-label use—half a pill of rifaximin with every meal because I don't want her to get food poisoning again because she already has the antibodies.

Dr. Pimentel: So, she goes to Costa Rica with this wedding party or whatever a group of 20 people. And they're touring the country on a bus going to the volcano, et cetera. But the bus is stopping at every restroom because 19 people on

that bus have diarrhea except for my patient who's the IBS patient. She was perfect the whole time.

The point being, the IBS patient was the healthiest person on the trip. No offense to people from Costa Rica. I love that country. I've been there. Somebody just ate some bad food there. And that was how that happened.

But 20 people, 19 people sick. The only person not sick, my patient. So it's just an example of how I use the antibody.

But I also tell people who have positive antibodies, "Look, make smart choices with food. You can't avoid food poisoning because, who knows, it could be from your grocery store, some recall. But chances are, if you cook at home, you're not going to get it. Chances are, if you eat at a restaurant that has an A on the door, you're less likely to get it than if you eat at a restaurant with a C on the door, reputable places. That's all I'm saying. Be more cautious. And people do!

And I have patients—my final comment is I have patients who, using the first generation test, rolling into the second generation test where, because of my advice—no food poisoning, no food poisoning, food poisoning—and their conscious choices, the antibodies have declined to the point where they don't feel like they're IBS is a big problem anymore. No more drugs.

And so, I know that if we keep the food poisoning way long enough, the antibodies will drift down.

Shivan: Okay, cool. So if you think you're having food poisoning, try to use rifaximin. Obviously, speak with your doctor. This isn't medical advice, you guys. This is just some ideas.

Dr. Pimentel: Right! So, what you're saying is a slightly different scenario. I was using it as prevention, but rifaximin is approved, FDA-approved, for food poisoning. So if you have food poisoning right now, it's FDA approved to take it. And the shorter the food poisoning, the less likely those antibodies are to rise up.

So again, that's very meaningful, very important. Get on it. Don't wait.

Shivan: And remember, one person's food poisoning is another person's gastritis I've observed. People are like, "Oh, I've never had food poisoning," right? What do you say to that, Dr. Pimentel?

Dr. Pimentel: Well, some people say, "Well, I don't remember food poisoning. And you're telling me food poisoning caused my IBS." The patient is in the office with diarrhea.

I said, "Well, what was your first day of diarrhea like?"

"Well, I don't remember."

"Well, the first day of diarrhea could have been just a mild diarrhea. You had to start at some point. And maybe that was food poisoning. You just don't remember."

The people who remember are their honeymoon was ruined. They were on a vacation, or they were in a hospital in a foreign country. Obviously, those are very—you know, they stick in your head.

But the test is very sound in terms of diagnosing that for you.

Shivan: Okay. And also, I went to a place called Any Lab Test Now. They drew my blood and sent it in. So, it isn't just about having to go to the doctor's office.

We're going to keep going, you guys. Okay, I'm going to kind of pop around. I'm going to do my best. I will say your first name associated with your question. So when you get the PDF at home, you can search by your first name.

So, there are a couple of people though that I've combined your questions. And this is general for Amy, Susan, Liz, Paris too, Ellen, Lorraine, Kim.

Dr. Pimentel, probiotics are no probiotics with SIBO?

Dr. Pimentel: So, this is a complicated answer, because I get sometimes criticism for my lack of enthusiasm around probiotics.

But I want to be very, very clear. I do not have lack of enthusiasm around probiotics. I have a lack of enthusiasm around the lack of enthusiasm by probiotic companies to put money down and do the proper clinical trials.

And so, show me a trial that has 200 people per arm—I don't want a massive drug trial, just 200 people per arm—that shows that it works in SIBO. And I will use that probiotic all day all night. That's my point.

So, the problem is we have small, little trials that aren't very well controlled. A lot of anecdote. There are probiotics—Bifida for example—that triggers the migrating motor complex. Does it trigger it in SIBO? Never been studied. Does it cause more bloating even though it's triggering? I don't know, never been studied.

[10:10] A study of 3000 patients. The only benefit you got from that specific probiotic was bloating if you took the probiotic.

Dr. Pimentel: So, I have not seen tremendous results with probiotics in my clinic except for anecdotes. So I do have some patients where they do get better.

So, I don't know if it's a good answer, but that's sort of where I'm at.

Shivan: So, Kim is asking about the *Bifidabacterium lactis HN019*. Are you familiar with these strains?

Dr. Pimentel: Right, exactly. So you go to your store, your general nutrition center, and you see a wall of probiotics. Some are in the fridge. Some cost $80, some cost $10. Is the $80 better than the $10?

My point is not against probiotics. I think probiotics are a future of this in a potential future therapy. But we need to figure it out. And I need better data. I'd be happy to study some of these. But I haven't been given many offers of funding for doing that. So that's the point.

I do see some patients get worse. I do see some patients get better. But it's purely anecdotal. And I haven't seen anything consistent.

Shivan: Okay. So Lorraine, I'm not going to totally get to your question because I think he just answered it, is that there are no studies to show that crowding out good or bad bacteria from taking probiotics can impact you long-term for your SIBO. So it needs to be studied is the bottom line.

Dr. Pimentel: There is one meta analysis in SIBO that they combined a bunch of little, tiny trials, and that combination of trials, in and of themselves, weren't very powerful. So somebody might quote that to me and say that "Well, do you know about this?" Yes, I do. But the problem with some meta analyses is that they take all negative trials, and all of a sudden, you get a positive trial. And again, my point is I think it has great potential, but I'd like to see more data. That's all.

Shivan: Okay. And I love that you're saying that *that* could be the future of it too.

Dr. Pimentel: Absolutely, absolutely.

Shivan: So, we just did a masterclass with Jason Hawrelak which was so interesting. It was talking a lot about strains and studies. And it's the Wild West, yeah. Lots to learn!

Dr. Pimentel: I mean, it may be very strange-specific. And that's Lorraine's question—I guess that was her name, Lorraine? It's very important. But I'd like to see the data around it to be sure. I don't want to cause any trouble for my patients.

Let me tell you… the ultimate probiotic fecal transplant in IBS caused harm. So placebo was superior statistically than fecal transplant in most of those very big double blind—relatively big double blind—studies, four of them, four trials. So that's the ultimate probiotic.

Now, some may argue that's not a good probiotic. But that is the ultimate probiotic. And it was harmful, not helpful.

Shivan: Okay. What do you think about people who keep getting negative SIBO breath tests but still have symptoms?

Dr. Pimentel: Negative breath test, but still has symptoms. So, this is really important because this is where we think hydrogen sulfide is going to be important. A flat line breath test, even a marginal elevated breath test that may be called negative or called borderline, it's probably because hydrogen sulfide is there, especially in the diarrhea side.

But even some of the constipated, we in the trial saw some patients who had both methane and hydrogen sulfide. And we think it's going to dictate the therapy.

But honestly, I can't tell you. People are going to ask me, "Well, what do you use for hydrogen sulfide?" First of all, that was a clinical trial, but it wasn't a treatment trial. So we don't have enough experience with the gas to be able to tell you what treatment works best. But we will have that within the next few months.

Shivan: Oh, that's huge. You're saying the next few years?

Dr. Pimentel: By the end of the year, we will at least in our clinic have tried various things and have a sense anecdotally. But of course, then we'll go on to clinical trials to try to prove all of this.

Shivan: So, that was for Marie and Christy and Tamara and Esther and Taza and Alexandra—Alexander.

So then, there's a lot of confusion around "Okay, I have hydrogen, but I'm constipated, and normally that's associated with diarrhea. I have methane, but I have diarrhea." Did I get that right? Yeah.

[15:20] There's all these like, "Well, I have this on the test, but my symptoms are opposite of what is usual based on…"

Dr. Pimentel: That is exactly why hydrogen sulfide is so important. We showed in the study—which will come out in a paper. We presented at the meeting, so it's public information—is that it's a tug of war between hydrogen sulfide and methane. In every patient, one of them wins the war.

Dr. Pimentel: They're warring for hydrogen. It's just like you have a lake. And you have two groups of people who are separate cities trying to eat the fish out of the lake. And whichever one gets the most fish is more prominent and so forth.

And so, in the individual where they have methane, but they have diarrhea, it could be that their hydrogen sulfide is through the roof. And hydrogen sulfide is winning in that patient even though they have a little bit of methane there.

So, that's sort of the information we're going to get once the new test is available.

Shivan: And then, is the treatment for the hydrogen sulfide the same as for hydrogen and methane? You knew I was going to ask you this.

Dr. Pimentel: Yes, yes. And I sort of expressed that, by the end of the year, we're going to have an idea on treatment. I think we're going to get there, yup.

Shivan: Okay, cool. Do you have an opinion—from Sandra—about which microbiome test is best? And do you see a value in that, speaking of over testing?

Dr. Pimentel: Well, I wasn't making that point in what I gave through the lecture part of it. But what I said in the lecture makes the point, is that the stool microbiome reflects nothing of the small bowel. And the small bowel really needs to be identified. And so, nobody actually has a commercial test for measuring small bowel microbiome yet. We're one of the only places in the world that's doing this in-depth analysis and setting the standard on how to do it.

So, that's the problem, is that you amplify a lot of things that are dead, a lot of things that have—

Just think about it this way. And I know this is really, really gross. But I'm a gastroenterologist, so for me, it's like dinner conversation. Think of a piece of stool. It's like a cylinder. The coating on the outside of the stool is the only thing that you see as a human because the bugs on the outside are

producing things that may be you get absorbed. But everything else on the inside, it's just between them because it doesn't escape the solid material.

So, the point is the majority of the bugs you're amplifying are dead. The majority of what you amplify is on the inside of the stool which isn't even relevant to you. So, it means that it's a whole warm mess, so to speak.

Shivan: Let's move on. I got it! Okay.

So, Karen and Marsha and Joanne and Anna, your information, your answers are in previous masterclass and Q&A recordings with Dr. Pimentel. So I'm going to keep going here.

Heartburn, Dr. Pimentel. Stephanie: "What is the best way to handle acid reflux when you're also trying to cure very stubborn SIBO since it seems reflux meds are counterproductive to SIBO clearing besides just avoiding acidic foods since I'm desperate to have a less restrictive diet?"

Dr. Pimentel: So, should we just cover diet in general?

Shivan: Sure, let's cover diet in general. And then, we have to cover like acid.

Dr. Pimentel: So, let's do acid then specifically because I'm sure there'll be other questions.

So acid's complicated because you need acid to help digest food. So there are some who say, "Well, you should take apple cider vinegar" or other things. You take those things, and that acid will help kill bacteria. And

that's absolutely true. So, exposure to acid, like the acid in the stomach for a very brief period of time, kills bacteria.

Then you take medications that suppress acid like PPI. Yes, that suppresses acid. And as a result of that, you can get some build-up of bacteria.

The problem with that is even PPI don't have 24-hour coverage. They say 24-hour coverage, but what they mean is that for almost all of 24 hours. But even five minutes of the potent acidity in the stomach, boom, the bacteria are gone because acid is very, very harsh.

And so, we don't see as much overgrowth as we would have expected just from acid. But yes, it does happen.

But the question is should you avoid acid, should you add acid. And this is really important for methane.

[20:02] In the study we did with PPI's, there was no more overgrowth with PPI's in IBS patients than those who didn't take PPI's. But what we did see is those with PPI's had less methane.

Dr. Pimentel: So, acid is hydrogen. It's an ion of hydrogen, but it's hydrogen. And the methanogens use acid to make methane. So, if you add acid, you fuel methane. If you take away acid, you reduce the fuel of methane production.

So, in people with methane, I would suggest actually a low acid diet. In people with hydrogen or non-methane, it's complicated because I don't

know what the hydrogen sulfide is because hydrogen sulfide also would use acid. So, it's complicated.

Knowing the breath test may tell you whether you should or should not do acid. If you're only hydrogen, acid is fine. If you're methane, try to avoid it.

Shivan: Oh, really interesting, okay. I wanted to let everybody know, anybody who is listening to this, because you've recently purchased this class, you will in your portal also have the last masterclass and Q&A's that we've done with Dr. Pimentel because I know there's no way for us to answer everybody's question in today's session. And I didn't want you all to be disappointed. I wanted you to have this information.

So, when you go and you log into your portal, it's all there. So that's why I'm skipping some of your names. And actually, I'm not doing the greatest job of saying your name with your question. But you'll get the transcript. So you'll be able to scour through all of this as well.

Okay, let me just get to—oh, the diet. Let's talk about diet. That was the other thing. So everybody wants to know about low fermentation diet while they're taking the medicines, the rifaximin or the herbals, to kill.

And by the way, just help us to finally, once and for all, discuss low FODMAP. Long-term or not? Thanks.

Dr. Pimentel: Okay. People listen to me really, really carefully; and sometimes, they listen to me too carefully. And sometimes, my words get extrapolated. And I don't mean for that to be the case because words can be black and

white. Even text can be black and white. But then there's more to the story. And I think, in diet, that's the case.

So, generally speaking, what I believe is that if you restrict calories—this is not belief. This is old science from microbiology years. If you restrict calories to bacteria, they go into hibernation. Some of them form spores, some of them wall themselves off to protect themselves from the environment and sort of brace themselves for a famine or dry times or lean times. And so restricting calories means bugs tend to be more resistant to antibiotics. That's true. That's very well known.

So, my philosophy is don't restrict calories to bacteria. Don't be on these low fermentation, low FODMAP diets if you're treating with rifaximin.

What ended up happening is people said, "Well, maybe what he means is feed them." And so people are doing guar gum and all these sorts of things I hear through the blogs and the Internet. People are suggesting maybe to augment. To be truthful, I don't do that. I don't augment. But I also can't say that isn't a good thing. I don't know. Maybe it is. Maybe it does help augment the effect of antibiotics. So you could be right, but that wasn't what I said, and that isn't what I do.

Now, in terms of low fermentation versus low FODMAP, we use the low fermentation diet, something we created here in like 2003 or 2004, long before low FODMAP became hyped. We didn't write a book about it, so it didn't get hyped as much. But the low FODMAP, to be fair, has done a lot

of science—which is really good—a lot of double blind studies and careful research. So It's a legitimate diet.

But the problem with the low FODMAP diet is it's highly restrictive.

And so, what happens is—there's two negative things that have been found with the low FODMAP (or three negative things). Number one, you tend to lose weight. For some people, they like that part of it. But it means that there's some lack of nutrition in it.

The second is that Bill Chey from Ann Arbor has shown that, after three months of low FODMAP, you actually can measure in the blood some nutritional deficiencies. So, that's the point why with the low FODMAP diet, you needs to start reintroducing at some point so that you don't get the nutritional deficiencies.

The third is microbial diversity. All we talked about in the microbiome conferences is more diversity, better biome—*more diversity, better biome*. So your biome is improved if it's diverse. But the low FODMAP diet has been shown to cause a severe reduction in diversity.

[25:16] So does that put you on a risk for infections? Does that put you at risk for inflammatory bowel disease? Nobody has proven that yet. But we have shown—or not us, but others have shown—that that's another downside of the low FODMAP diet.

Dr. Pimentel: The low fermentation diet is much more liberal. It's more meant to be balanced. You could go to a restaurant, you could probably find something

on the menu that is low fermentation without asking the waiter too many—

In my mind, I picture the patients all the time as front and center. They go to a restaurant, how irritating it is for the patient to be able to say to the waiter, "Well, does it have this? Does it have this? Does it have this?" Meanwhile, the rest of the company of that person is saying, "Wow, they're judging them on their selection." So I'd like a person to go into a restaurant, find something and not have to talk too much to the waiter because that's a better lifestyle and social experience for them.

So, I'm trying to make the patients as normal as possible, so they don't have to feel like a burden.

Shivan: Good! Sounds good. GERD, we just need some clarity about GERD. To PPI or not to PPI, that is the question. And GERD and SIBO.

Dr. Pimentel: Yeah, I mean if you have GERD, GERD is a risk factor for esophageal cancer in the long run. So you have to treat GERD. So I'm going to just say state that outright. You have to treat it in some way, shape or form.

PPI, we didn't find that it causes higher hydrogen in people with IBS. But in healthy people who have just plain old GERD, we do see some overgrowth developing that they didn't have before.

So, I don't hesitate to use GERD treatments. But I don't use PPI as a treatment for methane.

Now, my data suggests I could. If I put methane people on a PPI, the methane wouldn't go away, but it would go down. And so you could theoretically do that. It's not indicated for that. But I haven't routinely done so. But that's the other part of the PPI story.

Shivan: Interesting! This has to do with iron. Have you noticed the correlation between people will SIBO and low iron?

Dr. Pimentel: Well, with very bad SIBO, there's a couple of things that happen. B12 can go down. Iron can go down. But folate tends to go up. So, one of the markers for SIBO is a high folate because bacteria produce folate. We don't make folate. So we use the bacteria of our gut to help make it for us. So that's where we get our folate.

Shivan: So, if somebody's iron is low, and you give them iron or like an IV drip of iron, do you think that it will make their SIBO symptoms worse, or make their SIBO test more positive?

Dr. Pimentel: Iron isn't necessarily a growth factor for bacteria in the way that, certainly, we cause them to bloom or blossom. But the other caution about iron—first of all, iron therapies are very expensive, especially infusions. But the other part about iron is iron can also be deficient because you have a tumor leaking blood in your gut.

So, when we see low iron, we're more likely to scope somebody. And it's an appropriate scope because we're looking for something more sinister. So, just be careful that it isn't—or even inflammation can cause bleeding. Something could be leaking blood in the gut. And that's also very

important if the iron is low. So that's what we call a red flag. And we have to be cautious.

Shivan: Perfect! Okay. So, this has to do with treatment for methane because we haven't really talked about it in a capsule moment here. But a lot of people (Julie) are wondering about can you recommend another antibiotic protocol for methane-dominant SIBO besides rifaximin + neomycin, rifaximin + clindamycin, rifaximin+ Flagyl. She's unable to handle the side effects in the second line of antibiotics.

Dr. Pimentel: Yeah. So, first of all, the published paper—still off-label because it isn't FDA-approved for that—is rifaximin + neomycin. We've had good success with rifaximin and Metronidazole. We have not used, in our clinic, clindamycin with rifaximin. It sounds like her physician has.

So honestly, at that point, we do use some of the naturals. We do use—I'm blanking on it, but the commercial name is Allimed, the garlic…

Shivan: Oh, allicin.

Dr. Pimentel: Allicin… we do use that. And it does provide a reduction in methane, a temporary relief for some patients (although that wears off over time). We do try some of those in those patients.

[30:05] But we're holding out the best optimism for the SYN-010 trial. And of course, if she wants to participate, she lives close to Los Angeles, that might work.

Shivan: We'll get you that contact information everybody. Everybody is already asking about that.

Okay. Now, if you have the methane and hydrogen SIBO together, Barb is wondering what's your usual treatment program for that?

Dr. Pimentel: Methane and SIBO? I start with rifaximin plus neomycin, the off-label use, for 14 days. They have to take the correct dose—550 three times a day of rifaximin, 500 twice a day with neomcyin. And we do that for the full 14 days. What we notice is that it's between day 10 and 14 that you get the best effect—for reasons we don't understand. So you have to do the full 14.

And compliance is super important. So you have to take all the pills. It's a pain because there's a lot, but that's the only way to get it better.

So, that's what I start with. Of course, if it works, I still use a prokinetic after because methane, we want to try and keep it away as much as possible. We do use the low fermentation diet with maybe some caveats of reducing acid in the diet because I think that's important for methane. And some people can go a couple of months, but it tends to come back more quickly. But that's what I do as sort of the starting point.

Shivan: Okay. Now, if someone has methane and hydrogen, same thing?

Dr. Pimentel: If they're constipated, and any methane there, yes.

Shivan: That's where the symptom on top of the test results?

Dr. Pimentel: That's right, exactly.

Shivan: Okay, right. And again, the reason I know that is because he has talked about that in the previous classes which you have in your portal.

Let's see… these questions just kind of blew me away you guys. You're so smart. Christina: "Regarding the article *Susceptibility of Archaea to Antimicrobial Agents: Applications to Clinical Microbiology* in the Journal of Clinical Microbiology and Infection, why are squalamine and fucidic acid not commonly used treatments for methane SIBO?" That is an advanced question.

Dr. Pimentel: That is an advanced questions. So, we are looking at a number of therapies. And I can't tell you we haven't looked at squalamine because, of course, we have. And that paper is familiar to me. We've had such good success with lova—

So, in the first lovastatin trial, going back to the SYN-010, we saw that blocking the methane—first of all, blocking the methane synthesis isn't an antibiotic. What it's doing is it's impairing the bugs' ability to produce energy. As a result, it doesn't replicate as much. And so the bacteria that are around it, say, "Hey, the methanogens are not working so well." So they fill in where the methanogens were. And that sort of causes the shift.

And then, after three months, we have patients where the methane disappeared from the lovastatin. And even now, they're still back to normal. So, we think a new world order in the colon or in the gut occurs from lovastatin.

So, there's a lot of options we could have taken. And your viewer is very, very well educated on this topic. But we chose the lovastatin road. And so now we're sort of stuck in that road. But yes, I am familiar with the paper.

Shivan: So, I just want to talk about underlying causes for a second because people are saying, "Well, if I take rifaximin, and it only works for three months or less, what's the benefit?" They're like, "I took the drug, and then it got better in the short term. And then, it didn't work anymore" or "I relapsed." So, we're obviously talking about post-infectious IBS as one of the underlying causes.

But if you have like diverticulitis or you have blind loops or you have adhesions, just what's a strategy for everybody else?

Dr. Pimentel: Well, every strategy is different. If you have adhesions—like I give the example of somebody that I saw who was very distended, got rifaximin, felt great. One week later, it's back, got rifaximin, felt great. One week later, it's back. And this person had *never* in their whole life had surgery, never had any complication of anything.

And so, I did a barium study to look for adhesions. And sure enough, she had a sling around her ileum just pulling the ileum down into the right lower quadrant, angulating the ileum. And there was an adhesion there.

[35:14] The surgeon thought I was crazy because the patient was just miserable with this distension. The surgeon thought I was crazy that she would have an adhesion from nothing, never having had surgery in the past. He called me after the procedure. He says, "I've never seen anything like it. There

was literally sling. It took me one second to correct it. And everything returned to its normal place." And he said, "It was absolutely amazing to see this." The patient hasn't seen me in years now and has been doing very well.

Dr. Pimentel: But treat the adhesion if you can. The problem is if the adhesions are—you know, fixing adhesions get more adhesions in some patients. And so, it can be on a very vicious cycle where you're doing surgery after surgery after surgery.

I feel bad for those patients because some of those patients need to be on chronic therapy, chronic antibiotics. And I do have some patients on chronic antibiotics because of that. But there's no miracle cure for adhesions, not yet. And that's not one we're working on because it's a very difficult thing to solve.

Shivan: I'm going to be interviewing Heidi Peterson in Portland. And she does some things that are pretty naturopathic, neural injections and then there's Clear Passage. Clear Passage is in Gainesville, Florida.

So, a lot of people are trying a lot of things which is exciting to try to deal with adhesions.

Dr. Pimentel: I have used Clear Passage for some of my adhesion patients where I just don't want to do more surgery. But I guess putting my science hat on, again, the reason adhesions grow with time is because you're pulling and tearing, you're pulling and tearing, and more scar tissue forms. If we push

and tear more, do we create more? I don't know. I'm trying to wrestle with it.

But I do see some patients where, with visceral manipulation, they feel better temporarily. And then, they got to go back. But that same patient that had such a great benefit now has been in and out of the hospital with more adhesions. And so, who knows? Obviously, they're desperate. They need something.

Shivan: Yeah, visceral manipulation has helped me. I'm hoping that it sticks.

Okay, we're going to keep going here. What about brain fog? Anika is wondering about brain fog and treatment. Do you see that direct correlation between IBS SIBO and brain fog?

Dr. Pimentel: So, we see a lot of brain fog. And often, in methane producers, we see a lot more brain fog. And getting the bacteria or the archaea down in this instance of methane definitely helps brain fog.

Satish Rao has a very nice set of papers that are coming out. And he presented some work on even lactic acidosis from bacteria. But brain fog really is something we described in the book in 2006, even that brain fog really kind of disappeared when the bacteria went down. And patients really noticed that.

I ask that question less often these days. I'm not sure why. I really should get back on it.

Shivan: With the rifaximin, doesn't it also have a benefit for that liver condition, like the ammonia in the liver?

Dr. Pimentel: Yeah. So, rifaximin is used for hepatic encephalopathy which is a condition where the liver is failing and you're cirrhotic. And basically, the bacteria in the gut are accumulating and producing toxins, now the liver can't get rid of it because the liver's not working anymore. And so, those toxins overflow. Ammonia goes up as a byproduct.

But the rifaximin, what it does is it decreases the bacteria in the gut. And as a result, it decreases those toxins and the chemicals. And that helps the brain fog of the extreme which is hepatic encephalopathy.

Shivan: Okay, perfect. Let's see here. What it your experience with Atrantil, that supplement that Dr. Ken Brown has created?

Dr. Pimentel: You know, I've had some evolution of thinking around that. I mean, Dr. Ken Brown, his product has done quite well. And it seems to be that there is some effect in methane—or at least people are describing that. I haven't tested it formally in that way. But certainly, some patients do respond in terms of the bloating, especially with Atrantil. It's a combination of herbs that seems to affect the microbe in some way.

I'd love to study it more formally and maybe try to understand what's happening in the small bowel as a result. I think there's something there. I don't understand at all. And it doesn't work for everybody. But I think there's something interesting there.

Shivan: Carlene: "Do you have a theory, Dr. Pimentel, on why some patients have methane producers in their gut? Do you think it's genetics?"

Dr. Pimentel: To be honest, I don't think it's genetic. I think its environmental. So we often see, if mom has methane, daughter and son have methane. Look, your mother, your father are caring for you all their life. You're exposed to them and their microbes. And you're exposed to the food that they cook with their hands. We're not always perfectly clean. And so we share our organisms. [40:02]

Dr. Pimentel: There's a very funny study. This sort of speaks to this. People with dogs have more of a dog microbiome because the dog is constantly leaking their face. It's the same thing with humans. We're all living together, exposed to the same thing.

But I do see that if mom has methane, daughter has methane. And I have a lot of mother/daughter, mother/son, father/son kind of patients in the clinic.

Shivan: Dorothy: "If anti-vinculin antibodies are negative, should one still test for the anti-CDTB antibodies?"

Dr. Pimentel: So, it's a panel. So you get both.

Shivan: Okay. And didn't you say that the anti-CDTB is what happens when it's a little bit more acute? So those will eventually go down and the anti-vinculin will go up?

Dr. Pimentel: Correct, correct. You learn! Do you see? You were listening.

Shivan: I'm so proud of myself. Okay! I'm a patient just like you guys, right?

Okay… Donna: "Is there any relate between the archaea and methane gas production and ammonia in the gut or the bloodstream?", circling back to that rifaximin, liver connection.

Dr. Pimentel: Oh, specifically, bacteria in the gut equals ammonia?

Shivan: Yeah… interesting…

Dr. Pimentel: It's a little complicated there because if you talk to the liver doctors, they say that the amount of ammonia in the bloodstream is not proportional to the degree of confusion or brain fog. So they don't treat the ammonia. They basically just empirically treat. And then, the ammonia comes down concomitantly.

So, it could be that ammonia is really a surrogate of a particular group of organisms. And those organisms simply represent the fact that there are too many organisms around. But they haven't been able to say high ammonia equals brain fog, low ammonia equals no brain fog. That science has been studied immensely. And those connections are not linear. So there's not a line drawn between those two key factors.

So, sorry, that's a bit of a vague answer. But that's the facts.

Shivan: Taza, Susan, your post-infectious IBS questions, we have answered here.

Okay! Pam: “How do I know if I should do the IBS Smart test? If I already know that I have IBS, do I need it? And then, if I am positive, what would I do as a result?” That's a good question.

Dr. Pimentel: Well, people come in the office, and they have constipation, for example. And they say, “I’d like the IBS Smart test.” And I say, “Look, constipation category, it's not as valuable. So, I say I think it's probably not worth a look. If you want to spend the money, fine. But it's not really worth it as much as if you're on the diarrhea or mixed side.”

But what I tell my patients is, “Look, if you want to know where your IBS came from,” meaning it's from food poisoning, “And you want me to guide you on ‘Okay, if this is positive, you need to avoid food poisoning. And this is why…’”

Let’s say a patient comes to my office, and they have IBS, t hen they get food poisoning, and now they're way worse, I don't have a marker to tell me that they're way worse. So if I had that baseline marker, and they got food poisoning again, I know their IBS is way worse, I’m going to measure it again, and I’m going to say, “Look, this is what happened because of the food poisoning. You got to be more careful.”

So, in the end, it's going to get there. And that's what I'm excited about.

But if you're in the beginning of your IBS journey, this can diagnose your IBS instantly, quickly. So that's even valuable. But I use it in all my patients were it’s D or mixed at this point because I need to counsel them about food poisoning.

Shivan: Gotcha! So, Rick: "Are there other conditions besides food poisoning, particularly autoimmune, that could cause elevated anti-vinculin levels with the IBS Smart test. I know Gemelli Biotech has developed a scleroderma test that seems to rely on anti-vinculin antibodies. If so, would treatment just be prokinetics or other?"

Dr. Pimentel: So, the vinculin story with scleroderma, I'm going to tell you some new stuff but it's very hypothesis. But the patients with scleroderma have very high—like I mean very high anti-vinculin. So IBS, in the sense of SIBO, is a neuropathy of the gut. But scleroderma is an autoimmune neuropathy of the gut and the skin of the body. And so, we got the idea that "Well, maybe scleroderma is you've had vinculin antibodies for 30 years at very high levels. Maybe it's important to the development of scleroderma." And sure enough, the test was important—not important for lupus, not important for rheumatoid arthritis, but just specifically for scleroderma is what we saw.

[45:18] So then we did the validation, and it actually is a risk factor, or at least it portends that you could get some of the bad consequences of scleroderma. And these vinculins are very high in those patients.

Dr. Pimentel: But the point is it's on the spectrum, and that these anti-vinculin antibodies, when they're super high—

Look, I have a patient right now who she had IBS. I probably saw her in the year 2000. We didn't have a vinculin test. We treated her. She was doing well. And then, she started getting very autoimmune. And we were treating her as an autoimmune disease. Her rheumatologist in San

Francisco was treating her. And every time she got treated as an autoimmune disease, things got better.

She then started to get more intestinal pseudo-obstruction. And then I did the antibody, the vinculin, and it's super high. I think she has scleroderma now.

So, she started as IBS. Her vinculin could have been high all along. And now, 20 years later, we're seeing her. She's now got what it looks like scleroderma developing.

So, that's an example of how this antibody could be important even for the long run. And so whoever asked the question obviously has done a little homework on this. So we're very excited about these markers because they're going to help patients.

Shivan: Fantastic! Okay, more gallbladder questions. Would you recommend—let's see. There's pain in the gallbladder. So there's like people who have stones and sludge. There are people who have no gallbladder. And there are people who feel like they have low bile. They're just trying to figure out how that impacts SIBO and IBS.

What would you say to someone who has gallbladder concerns?

Dr. Pimentel: So, no gallbladder can lead to spillage of bile into the intestinal tract. So the reason bile—you know the bile diarrhea. Bile diarrhea is a well-known factor that can happen in some patients. And bile diarrhea is essentially

bile reaching bacteria, bacteria converting that bile into toxic bile acids that then irritate your lining and cause diarrhea.

Now, if you have bacterial overgrowth, the bile is going to see the bacteria sooner than waiting until it gets to the colon. So you're going to get a more pronounced effect.

So, bile acid diarrhea in somebody that has no gallbladder where bile is just dripping all day, you're going to have more pronounced bile diarrhea.

The problem with bile diarrhea is how to treat it because if you take like sequestering agents like *Questran* (or colestyramine is the generic name), you're [sopping up] bile acids , but it's very bloating, those products. So you could make your overgrowth symptoms more pronounced even though it's working very well for the bile acid.

So, the bile makes the condition and the situation very complicated. But I will say that if you treat the overgrowth, there's less bile interacting with bacteria, and it will lessen even bile acid diarrhea to some extent. So, I think it's a combination. It's a more tricky circumstance to treat those patients.

Shivan: What about parasites? We hear a lot in this group about—well, actually, we don't hear enough about it. But a lot of people have parasites or are suspicious of parasites or have never even considered parasites. They tried all these other things, it never works. I've heard other physicians come on and say, "Until you clear the parasites, nothing will work really to clear your SIBO." What's your opinion about that?

Dr. Pimentel: So, what's interesting is—and I'll just give one anecdote, and then I'll move over to the specific question. There are studies that show post-Giardia, you can develop IBS. Giardia has very high levels of vinculin in it, FYI. It doesn't have CDTB. It just has vinculin. So if you're killing that, maybe you're exposing yourself to vinculin. So that's an interesting anecdote.

But going on to the parasites, Giardia is one of the parasites. I've heard so many different things about parasites because they're hard to identify, you have to do multiple stools. Sometimes you don't pick it up. The expert is not a true expert. Some people send their stool to people who are, for example, experienced in Africa where there's so many parasites, and they can identify them better than we can hear because we just don't see them often enough. So, there's many complexities with parasites that make it very challenging.

But parasites is a very long story. One of the other problems is blastocystis, is that a pathogen or not. Some people say that if it's there, treat it, and that will help the IBS. But you're giving antibiotics, so you don't know if you're treating overgrowth, or you're treating the blastocystis. So it's a little bit mixed up.

[50:16] But there is some data on blastocystis being a mild pathogen in some patients. So, if I have a patient that I'm having a hard time treating, I might treat the blastocystis or some of the other parasites that are seen commonly and aren't typically thought of as pathogenic.

Dr. Pimentel: So, it's really patient-dependent on how I handle those things. But I don't measure parasites all that often, only when patients don't respond the way I think.

Shivan: Okay! We have 14 minutes left you guys. So I'm going to pop around to get as many things covered as possible.

From B: "A new study indicated a high risk relationship with lovastatin use in developing ALS or ALS-like symptoms. Are you concerned about that?"

Dr. Pimentel: So, there's some studies that suggest maybe statin use can generate a higher risk for diabetes and other things that are emerging in the literature. The point is that humans have been dedicated to making the statin get into your bloodstream. And getting this statin into the bloodstream is required in order to reduce cholesterol.

SYN-010 is dedicated to absolutely preventing it from getting into the bloodstream.

So, my hope or anticipation is that there are no consequences of something that just goes out in the stool and doesn't get into your blood. It doesn't affect your cholesterol. It isn't meant for that. So hopefully, none of the things that people are worried about will happen. And I understand the person's question.

The other part of it is cholesterol lowering is a chronic therapy. You have to take the status indefinitely to maintain the cholesterol. What we saw in the first trial was, three months, some of the patients where methane

disappeared never came back. That's what I hope happens. I don't know if that will happen. But that's what I hope happens in this trial, is that we drop the methane, and just a new world order occurs. And then you're done. Maybe in some patients, you do need longer therapy. But again, not absorbed and maybe it's only short term. Hopefully, that will alleviate the person's concerns.

Shivan: Great! What about this Keto diet? Somebody is asking: "Can a high fat diet cause methane SIBO? And if so, will a Keto diet be ill-advised?"

Dr. Pimentel: So, the complication of a Keto diet is that you tend to be more acidic because you tend to be ketotic. And so acid can fuel methane.

But a Keto diet also means more constipated because people tend to get constipated on Paleo and Keto. So, just by the nature of the food being ingested and the style of the diet—

It's hard to know whether it's the methane or just the diet alone that's causing their constipation to be worse while on the Keto diet. So I don't have a good answer for it. I've tried the Keto diet personally. I think it's pretty interesting. And it works for weight loss at least from my one-off experience. But it's just very up in the air because, again, the acid could be promoting more methane.

But we haven't studied it. I have no data. I can't tell you for sure.

Shivan: Brett, 12 years ago, he had a large amount of undercooked beef. He got severe GI problems, high blood pressure, pituitary level hormone

problems. He got miraculous temporary relief of all symptoms once after a mega dose of Flagyl, once after a round of—is it doxycycline?

Dr. Pimentel: Doxycycline, yeah.

Shivan: …doxycycline. "But I've never been able to duplicate that relief even with the same antibiotics. Can it occur that some antibiotics will work only once for certain GI tract conditions? Might Xifaxan work more than once for those same conditions?" Brett's never tried it. "And how can I understand the apparent effectiveness in a single patient of two antibiotics that target different types of bacteria?"

Dr. Pimentel: So, Brett's story is something we used to see back a decade ago before rifaximin where we would give doxycycline, it would work brilliantly, but then we could never give that again. We actually have a paper that shows how we gave a single antibiotic, neomycin (Metronidazole), and they would work brilliantly once. And then, try it again, it would never work. Even years later, trying it would never work because the bacteria become resistant to that one exposure. That's how interesting that was.

But rifaximin doesn't have that problem. You've given that, it works. It almost always works again. I can't say 100%. But 90% of the time, it will work again and again and again. And that's why rifaximin has been so beneficial.

[55:07] So, you could try rifaximin for the IBS or the SIBO that they have. It'd be interesting to see what that person's antibodies are too because food

poisoning started it from some raw meat. It might be interesting as to why it's tougher to treat for that person. And that's how I would approach it.

Shivan: I know we were talking about brain fog and SIBO and IBS. Maria is asking about straight-up depression and SIBO.

Dr. Pimentel: Yeah, so there's a growing bit of information about the relationship between the gut microbiome and psychological issues.

When I started the talk, I said stress is not the cause, depression is not the cause. But Nick Talley who is very, very prominent—he used to be at Mayo Clinic. Now he's back and he's I think the chancellor at a university down in Australia where he's from. But he showed that people get psychological issues after developing IBS, after the microbiome becomes derange. And there's a very, very prominent investigator in Europe (who I know very well) who is studying this.

And so, certain microbes can lead to depression or other symptoms—which is why, in our ReImagine study, as we're getting the juice, we want to know serotonin, we may want to know dopamine. We want to know some of the neurotransmitters that are associated with depression. What bugs are associated with that?

So, the answer is there is some connection, but we don't fully understand it. But it's being worked on heavily.

Shivan: Eleanor had a rectal bowel re-sectioning 20 years ago. Severe IBS resulted. Severe bladder infection. She was hospitalized for three weeks

with multiple antibiotics. Is it possible that she had a bowel infection that was undetected?

Dr. Pimentel: It could very well be. So, one of the things that you can get after a bowel re-section or when you're in the hospital and getting antibiotics for post-op recovery is C. diff. Sometimes it passes all on its own. So you go home and you had diarrhea for like a week or two, and you're just saying, "Oh, it'll get better." And it does get better. And that was the trigger.

I had a patient who had a hysterectomy. And she got antibiotics because she got a little infection just in the hospital. She took the antibiotics for three days at home. Everything got better. She got a little diarrhea after for about a week and a half. And then, ever since then, she got IBS. And I think that was probably a little C. diff. It wasn't that deep. And it went away by itself.

So, these are the things that people can have. And all of a sudden, that's the triggering event.

Shivan: Okay, prokinetics, here we go. Michael, we've covered what other prokinetics Dr. Pimentel likes or works with in his other masterclass.

Let's see…

Susan: "How long should a SIBO patient take prokinetics? And can it be life long?" That's a great question. They're all great, don't get me wrong.

Dr. Pimentel: Could you ask it again?

Shivan: Sure! How long should a SIBO patient take a prokinetic? And can it be lifelong?

Dr. Pimentel: Okay. So, the prokinetic is sort of an important part of the treatment, especially if they are relapsing frequently enough. I have patients who've been on, for example, the weakest of the prokinetics, which is erythromycin, at a very low dose, and I had them on that for more than a decade. And that works for them, and it's great. But if they stop it, then all of a sudden, things relapse.

But I try to get them off because my goal is to try and keep people as normal as possible. And hopefully, over six months, three to six months, we try and wean. And then, we see what happens.

Back in the day when we didn't use prokinetics, you give an antibiotic, the patient did great, and some people didn't relapse for two years with nothing. Some people relapse at two or three months.

So, I'm trying not to give everybody prokinetics. But certainly those that relapse, they're going to need something because, otherwise, we're giving antibiotics over and over, and I'd rather use the prokinetic instead.

Shivan: And so, what's your sign of relapse? Are you retesting after the round of antibiotics?

Dr. Pimentel: So, generally speaking, if the patient comes in and they feel great, they took a breath test, breath test positive, treat, breath test could be negative, they're great. If they relapse the first time, I might do a breath test just to prove that the relapse is really bacterial overgrowth. And then, I don't need

breath tests after that too much because the patient knows. They know what the relapse feel like. The breath test have correlated. And so, I just generally try and treat it.

If they don't respond to a treatment, let's say it's three years later, and we've been doing this routine, and they have diarrhea and it's a little different, it's a little odd, and it's not the same, then I'll bring them in and we'll talk through it to make sure it's the same thing. And then, we'll do a breath test again.

Shivan: Okay! I'm sorry I'm not responding because I'm reading to get in the last four minutes. It's Pat. Pat, he has answered your question about the risk of neomycin and Metronidazole in the last masterclass which you have in your portal my friend.

And that also goes for Anon. I don't know if that's you. Pat said that again, okay.

[01:00:16]

Shivan: Any suggestions on how to get rifaximin in a less expensive form—as in "how do you get it in a less expensively way" I think is the right way of saying it. Any suggestions?

Dr. Pimentel: So rifaximin less expensively?

Shivan: Yeah…

Dr. Pimentel: So, over the last two or three years, insurances have learned that rifaximin is—I think this is why. They've learned that rifaximin is costing less and

less because they're saving on the flip side on colonoscopies and other things. So insurance companies have been leaning towards paying larger and larger proportion of the bill for rifaximin.

However, I do understand that, in some cases, that's not the case. Ninety-eight percent of rifaximin is covered to some extent by insurance—which, boy, two years ago or three years ago, that was not the case either. I have no control on drug companies. So I can't…

Shivan: Have you heard of coupons? I've heard of coupons.

Dr. Pimentel: Oh, yeah, yeah. There are coupons you can get. You can call the company, Salix Pharmaceuticals, see if you can get some coupons or your doctor can. And that eliminates the co-pay for some patients depending upon your insurance. So there are ways to get it less expensive for yourself. So that's a way.

Shivan: Okay… is the IBS Smart test available in Canada?

Dr. Pimentel: According to what I heard, in the coming weeks, it will be. The answer is yes.

Shivan: Yes!

Monique and Kelly, good question about migrating motor complex. "Is taking supplements…" He's already answered this in a previous Masterclass. Do you want to just address that really quickly, Dr. Pimentel?

Dr. Pimentel: Say that again.

Shivan: If you're trying to rest your migrating motor complex for that four to five hour window… brushing your teeth, herbal tea. And is wine the same as food?

Dr. Pimentel: Wine is the same as food. But generally, I say water. I'm okay with some coffee. I'm okay with some non-caloric herbal tea. That should be okay. But anything with calories in it are going to cause trouble.

And don't put sweetener in it. Even though that's a zero calorie sweetener, the receptors of your body think its food even though they can't absorb it. So I wouldn't use sweeteners in your tea.

I hope that answers your question.

Shivan: It does. When it comes to leaky gut—huge topic to wrap up on here. We have one minute. Are you an L-glutamine guy? Do you try to help everybody with their leaky gut? Or do you just focus on "if you clear your SIBO, chances are your leaky gut is going to get…"

Dr. Pimentel: Well, there's actually a study that shows if you clear SIBO, leaky gut gets better. That's new. That's not our work, but others. So I'm really excited about that.

The other part is vinculin is part of the adhesion molecule complex. Vinculin impaired, your cells don't connect well. So it's possible that leaky gut and vinculin are related. We're working on exploring that question further to get you more data. So stay tuned for some more information on that one.

Shivan: Christine was asking: "Can you get methane in the stomach?" I think she's got some belching and gas issues. What would you say?

Dr. Pimentel: If methane slows the transit down of the small bowel and the colon, probably the stomach as well. But I don't think the methanogens are in the stomach. I think what's happening is the whole small bowel is slowed down to a point where the stomach is affected, and you get more belching.

So yes, it's probably related. I'm sorry to hear that. In fact, we did a factor analysis of methane versus hydrogen. And one of the things, belching can sometimes be associated with methane because of, we think, this reason.

Shivan: Oh, very interesting…

Dr. Pimentel, to honor our agreement of a hard out at the time we agreed to, I want to say thank you very, very much. Everyone, please chime in on the Q&A box with gratitude for this incredible SIBO hero.

Dr. Pimentel, if you do have the email address for anyone who wants to apply for the study… if not, you can email it to me, and I'll put it on the portal you guys.

Dr. Pimentel: No, what I'll give you is a telephone number to our research office. And please don't inundate. But it's 310-423-7302. They'll pass you on to the right personnel.

Shivan: Warn them, you're going to have to warn them.

Dr. Pimentel: I have to warn them.

Shivan: Yeah, you're going to have to warn them. I have the phone number, I'll put it in the chat in a minute everyone.

[01:05:17] Thank you so much, sir. We will see you in June with DBW updates. Looking forward to it. And I'll also see you in Portland at the SIBO Symposium in a couple of weeks.

Shivan: Perfect!

Dr. Pimentel: Thanks everybody.

Shivan: Thank you, Dr. Pimentel. Bye! Have a great day. Woo-hoo! You're a hero. I'm going to stay on, Dr. Pimentel. Have a great day.

Shivan: So many people are saying they have hope. I feel that way. I hope you do too. I just want you to know, if I didn't get your question, I worked really hard to cover as many as possible. We got to 99% of them. So, my heart goes out to you if you didn't. I know what that feels like. But I'm trying really hard to get to as many as possible.

Let me put the phone number in the chat. We do send your comments, by the way, to Dr. Pimentel. So you guys can—thanks Pat. We like to share the love with our speakers because it's a lot of work.

Thanks everyone for coming.

Hey Monet, Nanette. I'm glad you loved it. Steve, thank you very much for being a constant companion on this journey.

I also wanted to mention that if you do want to participate in the SIBO SOS™ Speaker Series for the 10 Masterclasses releasing in 2019, includes access to the Q&A with Dr. Pimentel on June 7th. The Speaker Series is currently only $19.80 per (because you divide the $198) class when you purchase as a series (individually Masterclasses are $59 each).

You would get instant access to the Masterclass with Jason Hawrelak. It's already happened (which was amazing). You get the recording. Please, if that is interesting to you, sign up for that. It is in the email we sent. Go to SIBOSOS.com, it's there. Email Karen at info@SIBOSOS.com. She will hook you up if you bought this thing for $59 and you want to upgrade. We will honor that.

Also, our next class is someone you probably never heard of before. Her name is Dr. Anne Hill. And she is out of Portland, Oregon. I was introduced to her by Dr. Tom Messenger—who a lot of you know love—and Dr. Allison Siebecker. And she's going to be talking about gut infections and parasites in this next masterclass that's coming up.

And we already have the class recorded. And we already have the Powerpoint—which, by the way, you guys, Dr. Pimentel said we could not get a Powerpoint from him. So, I don't know if he temporarily forgot that when he was talking, or if you might be like, "Oh, sure, I can do that." I don't I know.

I know, Martina, I didn't get to yours. But I'm going to try to figure out an answer for you on your question, Martina. If Dr. Pimentel will share the Powerpoint, I will ask him again. I think it's a legal issue with Cedar Sinai.

So I'll work on that. Just know it will be in the portal as soon as possible if it's available. But I don't think we're getting it. I think he was just kind of forgetting that in that moment… maybe.

Dr. Anne Hill is going to be on April 7th. This is the woman that Dr. Siebecker was in a conference and walked out of the conference to text me in the hall to go, "Oh, my gosh! You need to get Dr. Anne Hill for a masterclass. Talk later!" and then went back inside—so, just to give you an example of how enthusiastic she was and how much very special information she had. So it's something for you to look forward to.

And as you know, we are working on a 9-hour docuseries on IBS, SIBO and leaky gut. So we'll send out some Save the Date type announcements. I'm very excited.

The first part of the talk will not be recorded. I missed the whole—no, no, no. Lisa, it's recorded. I don't know what you mean by your question, sorry. All recorded.

There were masterclasses that we did late last year. In your SIBO SOS library, you will have them because I gifted that to everybody who signed up for this class because I want you to have as much comprehensive, cohesive information.

So you'll see what he's saying last year and you'll see how he's revealed even more information; and then, hopefully, even more information in June.

[01:10:08] A lot of people were asking questions that have already been covered in those previous recordings. And somebody was asking if SIBO was a lifelong condition. Honestly, it is and it isn't. It depends on your underlying cause. So that's just a new way of thinking about it if you haven't been thinking about it that way. Some people will have luck with rifaximin and neomycin or just rifaximin. If you have diverticulitis, if you have those blind loops—that's like a twist in your intestine, like that sling Dr. Pimentel was talking about—it might be lifelong.

Shivan: So, just for clarification, they're more underlying causes. So I want to say this.

Dr. Allison Siebecker, if you were not here for this at the end of last year, she did a class on underlying causes. If you do not know your underlying cause, please go to SIBOSOS.com and it's $59. It's going to be the best $59 you've spent. I really work hard to keep these recordings and these classes very inexpensive. It costs a fortune to do this—not your problem, but I'm just saying. Watch her class because if you don't know why you have SIBO, or if you're like, "I don't think I ever have had food poisoning," this class was incredible. It was her Sistine Chapel.

So, it's called *The Underlying Causes Masterclass with Dr. Allison Siebecker*. And our website is SIBOSOS.com. It's been renovated. It's so pretty. And of course, Karen's always there for you to help get you information and hook you up with the right links.

If you're not in the Facebook group yet, that's also about to be 8000 people strong. I saw the other day someone asked a question, 60 people

responded. And they were great answers. This is such an educated, compassionate group. I think it's the SIBO SOS™ Community Facebook Group. So you just go in there and introduce yourself. And then, you can pop in there. Even if you just sort of stalk it and don't even ever type anything, that's fine. There's a lot of good information there.

Rajna, don't worry, I gotcha. Email to Karen. Hang on Rajna. Eleanor, go ahead and do that. Good, B! I'm glad you're enjoying the work. Julie, yey, we'll pass that on. Kay, good to have you here.

And yes, hope is essential. That's one of the things. I don't want you to just have information. I want you to have inspiration as well. I have a lot of good information. But if I don't have the inspiration, a lot of times, I don't act on the information I know. So, I wanted to just let you know that's part of my whole philosophy and the team's philosophy. It's to give you information and inspiration.

Yay! Lor, Diane, yay, Gala, Denise. Hugs and kisses you guys.

Do you have to be on Facebook to join the the Facebook group? You do. You don't have to use your own name. Think about that. There are definitely privacy settings that you can use so that you don't have to have a huge privacy vulnerability. It's not perfect. It's the Internet. It's what it is. It's great until it's not. So I'm just putting that out there. I do want to invite you to it though. I know that we would love to have you there.

[01:15:16] We are bolstering up our YouTube channel. So, you don't have to be a member of the Facebook group to see some of the Facebook Lives and

videos that we post in the Facebook group. So when we do Facebook Lives—and I do at least once a month with one of these thought leaders—we are then putting it into the YouTube channel.

Shivan: And if you feel like this is all like over your head, then go and get the SIBO Underlying Causes course at SIBOSOS.com. Pick up a masterclass on Diet, Treatment and Prevention and Underlying Causes (which I've talked about already) and prokinetics with Dr. Siebecker. She did an amazing class on Prokinetics as well.

The name of the YouTube channel is SIBO SOS. I'm going to let my team answer that because I don't know if there's an underscore. I think if you type in "SIBO SOS," I think you'll find it.

I know, we did not get to the histamine question. If you're really interested in histamine questions, please look at—well, I think you've already emailed us Pat, and that you are already a patient of Dr. Leonard Weinstock. If you're not, that masterclass with him, that was a life-changer. "Since he put up the slide, the histamine is one of the things he is studying."

Lisa, he has addressed losing weight with methane, like a diet recommendation. Honestly, it wasn't like a life-changer. The methane does tend to eat more calories. And that's part of the problem. The methane literally absorbs more of the calories of the food we eat, which is one of the reasons why it tends to be something that does cause some people to gain weight. It wasn't like a "do this" kind of answer.

Definitely, Pat. I want Dr. Pimentel to study the histamines too. But if you need answers, Dr. Weinstock's class also at SIBOSOS.com, that changed my life. All these has changed my life obviously. I'm right here with you in it.

I know it's been an intense couple of hours. If this is your first masterclass, thank you for being here. Welcome! If this is your multiple masterclass with us here at SIBO SOS™, this is what keeps me going, these afternoons, these days where we get to really connect and get answers together. And this is what turns me on.

That's all there is to it. This is what stokes the fires of my enthusiasm. I didn't have this information. I want you to have this information. In 2015, I got that false diagnosis and had that false diagnosis for 18 months. I'm getting the timeline a little bit messed up. It doesn't matter. You get the idea. I was so lost. Remember, I probably had SIBO since I was five.

So, the fact that you guys are here just makes me feel like mission accomplished and makes me so, so happy.

Pat, time for a nap. Amazing energy and enthusiasm. But I'm telling you, this is what turns me on. I do a lot of other things in this lifetime. I have an amazing career. But you want to know what really, really gets me going?

And Karen and I started then studio back in the 90s together. And it's that same level of enthusiasm I have for you guys in these projects. So, just if you weren't here, we wouldn't be here. So thank you so much.

Doris, we're glad you made it into class under the wire, right before we started. I noticed you signed in. So, great to have you!

[01:20:04] Alright, I'm going to wrap it up. Everybody, go to SIBOSOS.com, get more information there. You can see all of the masterclasses we've done since last year. And if you are new, please check out Dr. Siebecker's classes. They are phenomenal.

Shivan: A lot of the questions that we were getting, I could tell they had not taken Dr. Siebecker's classes on diet, treatment and prevention, prokinetics and underlying causes.

This was amazing, obviously, and so hopeful. But I'm just saying that if you only do one other thing with us, get a hold of those masterclasses from Dr. Siebecker, and you will know more than your doctor—unless Dr. Pimentel or these speakers are your doctors. So, it's diet, treatment and prevention, prokinetics and underlying causes. They're so good. They're long, but they're good. Just take your time, breathe. We know that this is intense.

Rica, good for you. She's got an appointment at Cedar Sinai. That's awesome.

Okay, I'm going to sign off. Thanks everybody. We'll see you soon. Always find us at info@SIBOSOS.com if you need us. Karen is my best friend and a realtor. She's like this amazing, hey, power house business woman who also takes on this mission with love in her heart. She doesn't

really need to be doing this, but she does it because she cares about you too. So thanks.

Shivan: Thanks everybody. Remember, there is hope. Don't give up. Talk to you later.