SIBO SOS® SPEAKER SERIES PRESENTS

DR. MARK PIMENTEL

WITH SHIVAN SARNA & DR. ALLISON SIEBECKER

THE LATEST ON SIBO/IMO & IBS

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Table of Contents

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Shivan Sarna: Awesome! Hello and welcome! I'm Shivan Sarna here with Dr. Allison Siebecker of SIBOinfo.com fame and award-winning practitioner and SIBO specialist... and the incredible and one-and-only Dr. Mark Pimentel. I feel like Oprah right this second—you get a car, you get a car, you get a car. Sorry, I'm super jazzed as you can tell!

Dr. Pimentel who is head of the Pimentel Labs, the MAST Program at Cedars-Sinai, he is the one—no pressure, Mark—who I believe deserves Nobel Peace Prizes, Pulitzer Prizes, you name it.

I think he's going to be the one who cures us of this condition, small intestine bacterial overgrowth, IMO. I don't care what you call it. Just call me and let me know how it's going.

So, Dr. Pimentel, you're coming to us live right now from LA. Tell us about your background. What are we looking at?

Dr. Mark Pimentel: Oh, this is the new MAST Program behind us, all the new fancy, sciency-looking stuff. If you look way back there, that square window is where the lab is. We have about 8000 sq. ft. with all the sequencing equipment and everybody. I sort of tell people to shy away. But they'll walk around back there. We'll just let them do their great work!

Shivan Sarna: Do their thing! We're sending good vibes.

By the way, did I introduce myself? Hi, I'm Shivan Sarna, founder of SIBO SOS® and author of Healing SIBO. It's such a pleasure to have everyone join us. I did stream it last minute into our Facebook Group, the SIBO SOS® Community because we overflowed the Zoom cut-off of 3000 registrants. And the whole point is to get the word out. So, share this with your family and friends, your fellow gut sufferers.

I do want to adjust one expectation. We have been barraged with questions. And today, it's really about listening to Dr. Pimentel. So I am not going to be taking live questions. I bet you not to hate me. But this is a rare opportunity to hear from the doctor himself.

So, I'm going to let you take it away, Dr. Pimentel. And Dr. Siebecker and I will hide ourselves on camera (as well Clarissa behind the scenes). If anyone has any tech problems, please reach out in chat. That is exclusively for that. We will not be monitoring the chat or the Q&A for anything else.

If we have any naughty people here, which I doubt, be nice or be gone!

So, here we go! Thanks Dr. Pimentel for being here.

Dr. Mark Pimentel: Oh, thank you so much! And happy Valentine 's Day everybody.

[02:38] Presentation Overview

Dr. Mark Pimentel: So, I was asked to sort of give an update. But also, some of these slides, I used repeatedly because some things don't change, and some things change. But there are a lot of new slides because it's 2022 already and there's some really fascinating information.

But I'll try to put context or color around each slide so that you can understand why SIBO is the way it is. We call it the "new new SIBO" because SIBO continues to change, and new things are being added, and not to forget IMO, intestinal methanogen overgrowth. For those of you who tune into a SIBOcast and don't know what SIBO is, it's small intestine bacterial overgrowth. But I assume you all know.

[03:20] Research Recap

Dr. Mark Pimentel: I always show this slides because I think this is now pretty grounded. What we think is happening is that food poisoning—on the far left, acute gastroenteritis here—any of these four organisms could be the start, the trigger. You were fine until, boom, you had food poisoning. And for some of you, the listeners, one of the challenges we have is that "Oh, I don't remember food poisoning." Well, yeah, you may not because, 10 years ago, it could've been 2 days of diarrhea with E. coli after eating at some restaurant, but it wasn't so memorable. But then that's what triggered the whole thing. So you don't always have to remember the food poisoning for it to be a cause.

But the sicker you are with food poisoning, the more likely you are to develop IBS. And then, you follow this pattern of this toxin, cytolethal distending toxin (Cdtb) causes autoimmunity to the nerves of your gut, leading to the gut not working well... and then you get bacterial overgrowth.

And what I've got under here is all the proof that I'm going to show you during this presentation of how this all happens. And now IBS becomes an antibiotic-sensitive disease and how SIBO develops.

But I won't just talk about IBS and SIBO, I will broaden it a bit.

[04:32] What is SIBO?

Dr. Mark Pimentel: But what is small intestinal bacterial overgrowth? I wish, when I prepared this one slide the way it stands currently a number of years ago, SIBO is not exactly SIBO as it was in 2017 or even 2016. But we'll get into that.

But essentially, the large intestine contains a tremendous amount of bacteria per gram weight of stool. In fact, **half of the material in the colon is actually bacteria**.

But what I'm saying now is, in a little bit different context, even though there's so much bacteria in the colon, the bacteria only on the outside of the stool are you seeing as it's rubbing or touching the surface of the colon and interacting with you. **So even though there's a tremendous amount of bacteria, it isn't really affecting you so much**.

The small intestine contains a lot lower amount concentration of bacteria. But it's spread over 15 ft. of bowel that, if you laid it out flat and stretched out the villi, those little hairs that absorb food, it's the area of a tennis court. So imagine if you increase the bacteria in the area of a tennis court, it's like spreading a thin layer of peanut butter over a tennis court. That's a lot of peanut butter.

But the small intestine shouldn't contain more than 1000 bacteria per gram or per milliliter of material (whereas the stool, of course, contains a tremendous amount).

But before we get into this IBS connection because this is a lot of the thrust of our work, **SIBO occurs in instance in which the small bowel does not clean itself or clear itself properly**. So anything that causes the small intestine not to move, not to drain, not to flow fast—

The way that that works is food, you eat it, it sits in the stomach for about two hours… then it's gone. It sits in the small intestine for about five or six hours… max. Then it's gone. And it's in the colon for 24 hours or longer.

So obviously, more time, more bacteria because you have more time for the bacteria to grow.

We call the small intestine a relatively fast-flowing organ. Plus, it has a lot of fluid, so it kind of washes through. So you shouldn't have too much bacteria there—of course, scar tissue, adhesions, if you're taking narcotics (which paralyze in part the small intestine, you can get overgrowth), diabetes (especially if you've had it for a long time), and many other things.

But when we talk about SIBO, we often equate it to IBS because that's really the big chunk of the pie. **Irritable bowel syndrome affects one billion people worldwide**. And I'll talk about what proportion of IBS could be SIBO as there's more and more data accumulating.

But what we think based on culture—and I'll show you that data in a moment—is that **60% of IBS could be SIBO based on culture**.

Compare that with H. pylori and ulcer disease—H. pylori is an important bacteria that we now know causes ulcers. And this is if you take aspirin and Advil out of the equation. If you left it in, it would be 60%. If you take it out, it's about 73%. So it's not too dissimilar, these two concepts, that a bacteria, or a group of bacteria in the case of SIBO, is contributing to a very large chunk of irritable bowel syndrome.

Shivan Sarna: Dr. Pimentel, what was that with the Ibuprofen thing? What is that?

Dr. Mark Pimentel: So Ibuprofen is an NSAID. Any of those aspirins is an NSAID. And they can cause ulcers.

Shivan Sarna: Oh, got it! Thank you.

Dr. Mark Pimentel: If you took those out, if you put them back in, in other words, anybody with an ulcer, it's about 60%—which means that *H. pylori* and SIBO are almost exactly the same story. If we just looked at an ulcer, you saw an ulcer, about 60% of people with an ulcer would have H. pylori. And that's what we're seeing with the IBS.

So then there's the types of IBS. You have constipation, you have mixed, you have diarrhea types. And so, how does bacteria cause all these different flavors? And we now think that IBS is really sort of two flavors of microbe or bacterial disruption—one is the IBS-D and mixed, and the other is the constipation. But this group is going to get broken down. And I'll show you a little bit about hydrogen sulfide. But as we move towards later in this year, as things start to get published, this group is going to break into two potentially, and you'll start to see that.

[09:32] Could it Be SIBO?

Dr. Mark Pimentel: But it all boils down to: "Well how do I know if I have SIBO?" Well, you have to do some kind of test. You could do an invasive test and get a sample from the small intestine. But even that's tricky because they don't have the right kind of catheters. We have a catheter that we've developed that's not used in clinical practice. It's only for research purposes to get the juice from the small bowel properly and sterile.

But a breath test is a simple way of doing it without an invasive procedure. You would drink a sugar. And then, it gets into your stomach. It gets into the small intestine. And then, after that, the bacteria in the small intestine produce these gases that humans don't produce. It goes into your lungs and we measure it in your breath.

Allison remembers this, and Shivan as well… back in the early days of SIBO, breath testing causes IBS, or SIBO causes IBS. Well, we thought IBS is a disease of depression and anxiety and whether stress caused IBS. We now know that that's not true. There is no level 1 study that says stress causes IBS. Stress makes lots of things worse, including bowel function. So it's a modifier. But it's not stress.

But imagine the early days of this where we were saying, "Oh, bacteria caused IBS" when everybody else in the past thought stress and anxiety were the contributors… it was controversial.

But now, fast forward to 2020, these are 25 studies. Without a doubt, SIBO by breath test is more often causative in irritable bowel syndrome. And so, full stop, we now know this to be true.

This just came out from scientific reports. And this is an important finding because, if you just did a good study on irritable bowel syndrome, what proportion of patients would be positive on a breath test? Well, of course it varies. And those who are more used to seeing these types of patients, including us, we're seeing higher rates.

But in the general usage of breath testing, it is very typical to be about 49% or 50% of patients positive. So one of the concerns is that there are some people who get much higher results. Either they are real experts, and they've got a referral practice sort of like us where they get more of those types of patients. But if it's too high, you've got to be concerned. But we're seeing, on average, 50% of IBS is SIBO based on breath test from this meta-analysis.

The point of this is not what percent you're going to have in your practice or a doctor will have in their practice. The point of this is… SIBO is a big part of IBS. It's at least 50%. And by culture, it's 60%.

So, the point is SIBO and IBS are intermixed. And we think SIBO is causing IBS.

So these are the gases we measure on a breath test. **Hydrogen** is one of them. In fact, that was the original gas when the first breath test started in the 1970s and '80s. Hydrogen is not produced by humans. So if you find hydrogen in the breath, it's coming from bacteria, somewhere in your body—and in this case, we now know it's the gut.

But that's the simple part of the story. It is not simple because hydrogen really doesn't do much. Yes, it's a marker for overgrowth. Yes, you can diagnose overgrowth. **But you could have a 200ppm of hydrogen on your breath or 30, and you still have SIBO**. And the 200 patient is not worse than the 30 because hydrogen is being used. It's a fuel for other organisms, methane-producers, for example. And they take four of these hydrogen to make one **methane**. And then, hydrogen sulfide-producers take five to make one **hydrogen sulfide**. And those are the other two big gases.

Here's the problem. Breath testing, up until the last year and a half, only measured hydrogen and methane… and only in the last year and a half can we measure all three at the same time. If you don't measure all three, you're missing the whole story. And you'll see more papers come out this year by us that tells you why it's so important to measure all three. And the whole story is just bigger than just hydrogen and methane.

But before I run off that topic, you've got small bowel culture. These are the culture studies. So this is not breath test anymore. Even in these culture studies back in 2007, 43% of IBS had SIBO. In this study in 2012, using the 1000 bacteria cut-off, this is the

60% that I told you about earlier. So if you have IBS with diarrhea, there's a 60% chance SIBO could be causing your symptoms. And so it's super important to know, look and then treat because you could be treating a causative factor in IBS.

But now, where the work is heading is... it's one thing to say you have SIBO. It's another thing to say, "Well, we could try these treatments." It's an even greater thing to say, "We know who it is... we know where you live... and we're going after you." And that's where we've been for the last six years.

We now know it's *E. coli and* it's klebsiella. And I'll show you later... we now know where they live. And some of the drugs weren't getting there as well as we'd like. And so that's where we're developing new programs for treatment that are hopefully going to do much better.

Another culture study, this is from Australia. Is anybody from Australia out there? This shows, again, functional GI disorders. So that's what GID stands for. But the majority of those patients were IBS, some were dyspepsia patients. It doesn't matter. Both groups had higher bacteria in their small intestine.

The argument I'm trying to make the evidence is pretty overwhelming at this point that SIBO and IBS are intertwined, whether you look at the breath test, and whether you look at culture. And I'll show you in a minute the most sophisticated deep sequencing of the small intestine... same thing, same result.

[16:05] The Small Intestine Microbiome

Dr. Mark Pimentel: So now, we get into that sophisticated stuff. This is the REIMAGINE Study. We hoped to do and where we're seeing the fruits of our labors starting now is that the REIMAGINE Study was where we should be looking for the microbiome we

think is the small intestine. It's that peanut butter spread across the tennis court. That's the surface area of the small intestine. That's the absorbing surface of the gut. Imagine what the bacteria can do to you if they're wrong there.

We're looking at various diseases—obesity, of course SIBO, various other conditions, even autoimmune diseases. And stay tuned for some of those interesting results that's already emerging from our lab. And you'll start to hear that in the medical press soon.

But back to just focusing on SIBO. The REIMAGINE Study helped us even further define SIBO. This is a SIBO patient. This is a patient with cultures showing SIBO of the small bowel (this is not just the breath test). And this is a non-SIBO patient.

And right away, you see this orange bar that's much bigger here than here… that's ***proteobacteria***, which, when you boil it down, is ***klebsiella*** and this gray bar is ***E. coli***.

Where is *klebsiella* and *E. coli* here? This little tiny sliver, and this sliver. Nothing! So SIBO is all about *klebsiall* and *E. coli,* getting down to who the bad players are here.

I know this is a complicated slide. But the evidence for all of these needs to be built because critics have come along and said, "Well, yeah… but breath testing is not that great." Then you do culture and they say, "Okay, well, you did culture. But maybe the breath test is showing you that the lactulose sugar is getting to the colon. And that's where the hydrogen is coming from. And therefore, the breath test is not good." Well, that's not true either.

So here, we did sort of a metabolic function of the juice of the small intestine. And what we see is that the breath test correlates—that's hydrogen on the breath test—with all the mechanisms and enzymes that bacteria have to produce hydrogen in the small intestine. So the juice in the intestine has the gears to make hydrogen. And that correlates with the fact that, yeah, you have hydrogen on your breath test.

The point of that is the hydrogen is not coming from the colon. It's coming from the small intestine, full stop. So that argument is done.

But there's a couple of very complicated—but not really—elegant diagrams. This is what your microbiome network looks like in the small intestine. So think of it like Los Angeles. You have a city. You have plumbers, doctors, lawyers, sanitation workers, you name it, in harmony, in the right amount of each so that everybody makes enough to live, and it's a harmonious situation. That's what normal looks like. So everybody is of relatively equal proportions. And they all interrelate very harmoniously.

I put two circles—one is *E. coli*, the other is *klebsiella*. Remember the two characters I don't like, the ones that are causing SIBO? They're nice and balanced with everything else. But looks what happens in SIBO. Look what happens to the harmony. It's gone.

This is *E. coli* now. *E. coli* is up. *Klebsiella* is up. And they just destroy the rest of the microbiome. They're less cohesive. They're less interactive. And there's bad actors adding on top of it.

So, this is what happens in SIBO. This is what your microbiome looks like if you have that condition.

We worked a little bit with Rustem Ismagilov from CalTech. And he proposes this microbial hysteresis. The *E. coli* is the bad disruptor. And it goes up and up and up. And it's fine! Your gut is able to handle a little bit of *E. coli* and a little more *E. coli* and a little more *E. coli*... until you reach a tipping point. And then, it flips. And when it flips, you're in an unhealthy state like you saw in that last picture.

A little complicated slide, but the point I'm trying to make here is that... somebody said, "Well, you keep saying that adhesions cause SIBO, but I can't find a paper." This paper literally just came in 2021. They created sort of an adhesion model in an

animal. But there's two points to make here. If you have adhesions in an animal, you get SIBO. Okay, that settles it. It's true.

But the second thing is, when they got SIBO again, it's E. coli, *Eschirichia coli*. That's the genus that's going up. And it's similar to what we're seeing in IBS.

[21:07] What is IMO?

Dr. Mark Pimentel: Okay! So now, let's talk a little bit about this methane thing or intestinal methanogen overgrowth. Now, people say, "Well, why did you break SIBO into SIBO and IMO?" Because methanogens are not bacteria. So the B in SIBO, "bacteria," doesn't fit.

Secondly, methanogens live in the colons and the small intestine. And they can be elevated in the colon in an abnormal way, causing symptoms. So the "small intestine" part of SIBO also doesn't fit.

So we had to create a new term called "intestinal methanogen overgrowth." And that's where we stand.

So, things are going to change on this slide a lot because we've learned things in the last few weeks that changed this slide. But as of now, I can't because we haven't published it yet. But you'll hear about it in probably the next two or three months.

The actor that's producing hydrogen from methanogens... I thought it was E. coli. Yes, E. coli produces hydrogen. But in this situation, it's not this one. That's all I can tell you for now. You'll have to wait to hear more. But we figured out who the characters are that are feeding this *M. smithii*.

M. smithii is the methane producer. It is an archaea. It's not bacteria. And it produces methane. **And the more methane you have, the more constipated and bloated you become**. And so this is really important.

So, this is a meta-analysis of methane and constipation. And clearly, methane causes constipation by breath test.

Now, I wanted to put this in sort of like a summary of what we've talked about so far. But you have to think about in a different way. Think about it in the year 1999 when we were first publishing our papers on this way back then when IBS was thought of as a psychological condition. And even up until the last few years, there were still some, "Well, could it be… could it be… could it be SIBO?" And now, we've got one of the world experts in IBS publishing a paper just last year saying, "Yup, a subset of patients with diarrhea-predominant IBS have small intestine bacterial overgrowth. Yes, methanogens, these bugs that produce methane, are associated with constipation and can be treated with antibiotics. And yes, antibiotics can be effective." And they talk about diets and other things including rifaximin.

So, things have changed dramatically in 20 years. But it took a lot of work.

[23:42] Hydrogen Sulfide SIBO

Dr. Mark Pimentel: But the new kid on the block—so this is now going past all of these—is hydrogen sulfide.

Now, one of the characters for producing hydrogen sulfide we now know is ***fusobacterium***. And ***varium*** is one of the species. But there are others like *desulfovibrio* and others (which are beyond the purpose of this talk).

But when they use hydrogen But when they use hydrogen to produce hydrogen sulfide, we now know that's the reason you have diarrhea urgency and pain—not the hydrogen. It's this. So if you don't see this, you don't know everything about the patient's breath test.

So, we wanted to, for many years, add hydrogen sulfide to the breath test. Here's the problem. Hydrogen sulfide is very reactive. It's not stable. And so you have to keep in a container that is rated for holding hydrogen sulfide, hydrogen and methane for periods of times, so that you can send it to a lab and have it measured. And so that had to be worked on. And we've solved that problem.

Hydrogen sulfide also needs special sensors—but not just a special sensor for hydrogen sulfide. You have to have hydrogen sulfide, hydrogen and methane all in the same instrument measuring the gases simultaneously without cross-reading other gases.

So, maybe the hydrogen and hydrogen sulfide would be read as hydrogen a little bit on the hydrogen sensor. And if it is, you have to adjust for that. So there's a lot of technical difficulties.

And then, you have to do the clinical trials for that instrument, for that bag system to make sure that it correlates with the human system. And we did that. Initially, the cut-off was 5. And now, the new cut-off is 3. But it's for a reason. And I'll show you why in the next slide.

But looking at the test compared to old tests, the new test is exactly the same as the old test for hydrogen and methane—maybe a bit more specific because the new sensors in the new test are within 0.1ppm, and in the old tests, it's ±2. So the error is 2ppm. That can be important if you're hovering around 19, 20 being the cut-off, because if you're 19, maybe it's really 21. If it's 21, maybe it's really 19. And that's the

difference between a positive and a negative test. So, having a more accurate, more precise measurement can be important.

So, the first look at these data was, okay, let's take real diarrhea patients, flat-out diarrhea. And sure enough, anything over 5, really, this was the diarrhea group. But we've since looked at a group of IBS-D patients, and they're down here because they're not as severe diarrhea, and more than 3 is a good cut-off for them. So 3 is the new cut-off.

This is a hard figure to understand. But the point of this figure is, with methane, the more methane you have, the more constipation you have. With hydrogen sulfide, the more hydrogen sulfide you have, the more diarrhea you have. Whereas with hydrogen, it doesn't matter—high hydrogen or low hydrogen, it just is there or not. So that's why **these two gases, methane and hydrogen sulfide, are like the thermometers of your symptoms, whereas hydrogen is just the fuel for these other two thermometers**. It's just important to have all three gases.

Cool study, we presented this last year. This basically proves that this bug, *Fusobacterium varium,* we put them into the rats, the rats here produce more hydrogen sulfide. And because they produce more hydrogen sulfide, they got more diarrhea. And when the bug cleared out, the diarrhea went away. That's it! As simple as that… this bug, hydrogen sulfide, means diarrhea.

[27:40] SIBO/IMO & IBS Treatments

Dr. Mark Pimentel: So, how do we treat SIBO? This is really important. We got to transition from all these great science to "well, how do we make it better?"

Well, this was a study looking at rifaximin. Rifaximin was conceived on the notion that IBS was a microbiome disease. We didn't have as much of the details we do now that have been filled in. **But rifaximin has been the best drug ever for irritable bowel syndrome with diarrhea**. You take it for only two weeks, and you can get months of benefits. And that's what we saw. This is just the initial study showing everything got better. Everything to the right of this line means statistical significance. So it didn't matter what you looked at. Pretty much, the patients were better. And it lasted for up to three months.

But since then, we did another study in terms of rifaximin showing that, okay, so if you took rifaximin, and you had no idea, 44% of people would respond to rifaximin using a very difficult FDA end point.

But look what happens if you add the breath test. If your breath test is negative before you take rifaximin, you still can respond, a quarter of people, but much less. But if the breath test was positive, 56% of people respond… a lot higher. And 76% of people are responders if that breath test was positive and rifaximin made it negative.

So, it speaks to the importance of the breath test. It speaks to the importance of identifying SIBO and being able to know who's responding because, if that breath test doesn't become negative, that people won't respond. And that's the point.

Now, **methane** is a different animal. It's not a bacteria. It's an archaea. And an archaea are ancient organisms. We didn't design antibiotics for archaea. It happens that some of these antibiotics do have some effect. But you need more than one antibiotic to get it done.

This study, these are constipated patients. And of course, they're constipated because they have methane. And we gave them neomycin (this is an antibiotic) with placebo. Not so great! This is the constipation score. It's still a pretty high score for

constipation. But the score is much lower if they got the **neomycin + rifaximin**. And that's what we do traditionally with IMO, intestinal methanogen overgrowth.

Hot of the press! People wanted to know, "Well, how long do you have to take these antibiotics for the methane to go down?" The methane starts to go down by about day six. But it really is 9 to 10 days before it really goes down to that less than 10 mark. So we generally recommend 14 days because **you need the full 14 for the methane to go down**.

The other thing in this paper that just came out is we really show that, even though we weren't necessarily in the North American Consensus agreeing with 10ppm, 10 really is the widest spread. The constipation score is much higher if you have 10ppm and less so if it's 5ppm. Ten parts per million probably is a better cut-off for identifying methane or relevant methane.

Hydrogen sulfide is the new kid. So we don't have a lot of randomized controlled trials or treatment data yet. But what we do know from as early as 1998, **if you take Pepto Bismol—that's the marketing name for bismuth—with your antibiotic, you can really reduce hydrogen sulfide**. And that's what we're doing in the clinic. But we're waiting for some clinical trials that are coming right now on some new products that are really hopeful for treating all of the above actually, but especially hydrogen sulfide.

[31:41] Getting to the Cause

Dr. Mark Pimentel: So, in the last segment, I'm going to spend just a few minutes switching gears and saying, "Okay, you have SIBO. You have IBS. But how the heck did this start? Why do I have this? Is it my genetics? Is it something I did? What's going on?"

And we now know—this is a Mayo Clinic study from 2017. They'll probably do another study coming up. But there's 45 clinical trials in this study. **One in nine people who got food poisoning now have IBS**. So we now know food poisoning causes IBS, full stop. And that's what we've been working on for now, about 15 or 16 years, with our animal models.

What we eventually want to do is not to treat SIBO with antibiotics. That's the short-term game because we want to help people get better. The long-term game is: why is this happening? What's the driver? And can we cure IBS and SIBO by getting to the root? And that's really what our focus is on in the lab also.

This is an animal study. We basically gave these rats *campylobacter*, campylobacter food poisoning. After food poisoning, 27% of the rats developed IBS—a lot more than humans. Humans were 1 in 9. This is 1 in 4. But we gave them a good amount of campylobacter, a large amount. So we're pushing the limits, and we're getting 27%.

But the point is… food poisoning causes SIBO which we know is associated with IBS. Not just that, if the rats got the campylobacter (which is C+) and got SIBO, those rats also had altered bowel function. So they got IBS-like symptoms. They also had a little bit of elevated white blood cells and lymphocytes in the rectum when we did biopsies. That is also what's seen in humans.

Why am I showing you all these really hardcore data? Because the animal studies we now have, and the animal models we now have are identical to what happens in humans who develop what we call *post-infectious IBS* and they develop SIBO. And so that's putting the two things together.

[34:00] The Mechanism Behind Post-Infectious IBS

Dr. Mark Pimentel: I'm fast-forwarding probably 20 studies, but it all comes down to this talk about the **cytolethal distending toxin-B (CdtB)**. *Campylobacter* has it. *E. coli* has it. *salmonella* has it. And *shigella* has it. It's the only toxin they have in common.

We then took that toxin, purified it, and gave it like a vaccine to rats. So, all the rats saw were this toxin. They didn't get food poisoning. They just got the toxin. But guess what? The rats got SIBO. I'll show you.

First of all, they develop antibodies to this toxin. That's expected because we're injecting the toxin. But they developed the antibodies to themselves, **vinculin**, which is a protein in the nerves of their gut.

So getting this toxin meant that they got antibodies to themselves. That's called an autoimmune disease. So this toxin causes an autoimmune disease to the gut nerves.

Focus on this side, this bar is down here. This bar is up here. The rats who got this toxin now have SIBO both in the duodenum and the last part of the small bowel. This line is higher than this line statistically. They got SIBO. So this toxin, all by itself, causes SIBO.

Just a little education on vinculin... these green lines here are the skeleton that holds your cell in shape, especially nerve cells. And this red—you can see it better here—these red tufts are vinculin. And they are like a little motor at the end of these lines, the green lines, that causes the cell to reach out grab on to the next nerve cell so that the nerves are all connected. **And when you disrupt that, the nerves get disconnected.**

So, the way now we think IBS is working is you get exposed to this toxin, and then you develop antibodies, and the antibodies don't like this part, don't like this part, don't like this part, but this part looks a little like vinculin. And you get autoimmunity. And that's called **molecular mimicry**. This toxin is mimicking vinculin on purpose so that you develop this immunity to yourself, and then you cause this damage. But it helped us develop a blood test for IBS.

If you look here, this is IBS in red. This is the CdtB antibody in your blood. It's way higher than in Crohn's or ulcerative colitis or other conditions of diarrhea. Same for vinculin.

If you're positive on both blood markers, you have a 98% chance for IBS. You do not have to do other tests potentially. Specificity is over 90%. And this is really, really sort of the important part of this test.

So, this is the sequence. We're coming down to the last few slides. You have food poisoning, you get exposed to this toxin. It can create autoimmunity. That autoimmunity damages the nerves of the gut. That damage to the nerves of the gut means the gut doesn't flow correctly—remember not flowing enough? Bacterial overgrowth. Sure enough, that's what happens in the animals. And that's what's happening in humans. And then, IBS becomes an antibiotic-responsive condition.

This just got published. I'm excited to put the citation at the bottom. But this shows the whole thing I've been telling you about. You have this beautiful bacterial colonization of the gut, all the different colors, so many different types of bacteria all living in harmony. The nerves of the gut, everything is intact. And the gut flows correctly.

Then this invader, Campylobacter in this case, comes in, causes food poisoning. It produces a toxin that you get exposed to. And then, you produce antibodies to this toxin here. And you can see the antibodies to the CdtB go up first. And it takes about

three months for this anti-vinculin to start. When the anti-vinculin starts, you start to get a breakdown of some of the nerves. And then, you get poor flow. And then you get a build-up of these blue guys which are the E. coli and klebsiella. That's how SIBO happens right here on this slide.

[38:16] Clinical Implications of the Research

Dr. Mark Pimentel: So, how do I do this? How do I do this in practice? How do I use the test? What do I do to try and treat patients?

Based on all these evidence, if you have a patient with chronic diarrhea—I'm not saying IBS here, I'm saying chronic diarrhea—I want to know. Chances are they have IBS because that's the highest likelihood. But let's figure it out more precisely.

If you have anti-CdtB and anti-vinculin positive, you have IBS. I'll do the three-gas breath test also. So if you're positive, more than 90% specificity, this is irritable bowel syndrome.

Well, you say, "Maybe I just do the gas breath test because the gas breath test tells me how to treat." Yeah, but if you know it's food poisoning, I can tell you... you're more likely to get food poisoning again because of the nerve damage. So I want my patients to know because, when they travel, they take more precautions. They're aware of what caused everything for them.

Now, if it's negative, and the breath test is negative, you need to think about what's going on because something else is going on.

But if the three-gas breath test hydrogen is positive, then I'm giving rifaximin. Now, with the new hydrogen sulfide, I'm giving rifaximin with bismuth. We're waiting for some really interesting double blind studies to be available for public scrutiny. That

will show some really interesting results with hydrogen sulfide. But for now, this is what we're doing.

Mixed constipation diarrhea, I do the same thing.

For the chronic constipation, you can either do the three-gas if that's convenient, or two-gas because you have to focus on methane here. If your methane is positive, we give rifaximin + neomycin. If methane is negative, think about what else is going on because something else could be going on.

And then, you can substitute neomycin for metronidazole if you're worried about neomycin and some of its side effects.

[40:13] Conclusions

So, here's the proof of SIBO & IBS. And this is my last slide. Proof of SIBO: here's IBS, here's SIBO. What we know is there's 25 studies that prove that breath testing is important in IBS.

What we know is there are four studies proving SIBO & IBS by culture and 60% of IBS-D is SIBO.

What we know is breath testing now is validated by sequencing and culture using specialized protective catheters.

What we know is hydrogen on breath test is produced in the small bowel. And this is based on metabolomics.

Antibiotics make IBS better.

And so we know this story is pretty complete. We're just trying to further it with the IMO and the hydrogen sulfide.

And improvements in IBS depend on antibiotics.

So, in conclusion, IBS is commonly a small bowel microbiome disease.

SIBO is an important contributor to IBS.

These are the bugs. These are the bug actors that really cause a disruption in your bowel—*E. coli and klebsiella*.

Methane is associated with constipation. That's now clear.

Hydrogen sulfide is becoming clearer and clearer by the day as the missing link in diarrhea that we couldn't figure out before.

Reducing methane makes constipation better.

We need better treatments. So now that we understand the microbiome better, and where these bugs live, we're already doing better. And you'll hear more about that in the coming months.

And then, autoimmunity is super important to all of these. The CdtB and the vinculin and the antibodies to these are helping us unravel the *true* root cause.

Now, treatments for these antibodies are being looked at right now. And we're trying to figure out that. **That will be the true cure**. But that's going to take a little bit more time.

I'll stop there and open it up for any questions. Thank you very much.

Shivan Sarna: Oh, thank you so much, Dr. Pimentel. I know Ramona, for example, a long-time follower of yours and ours, is in her house right now jumping up and down when you just said that about the antibody treatment—as I know so many of us feel that way after taking the Trio-Smart™ test—or not.

[42:32] The ibs-smart® Test

Shivan Sarna: Can you just describe the Trio-Smart™ test a little bit more for anyone at home who's wondering, "Do I have these antibodies?"

Dr. Mark Pimentel: Oh, the ibs-smart™ you mean is the…

Shivan Sarna: The ibs-smart™ test, sorry. Thanks! Trio-Smart™ is the three-gas breath test. This is the ibs-smart™ test. Thank you.

Dr. Mark Pimentel: Yes… so ibs-smart™, basically, the kit gets sent to your house, or you can get it from a doctor's office, or a practitioner's office. And then the blood is drawn and is sent back to the lab. It basically just measures these two antibodies and how high they are in your blood. And if they're at a certain level, that's what's causing it.

Now, one thing I didn't talk about is that **the anti-CdtB antibody tends to go down with time** because if you don't get another food poisoning, you don't get that juicing up of the antibody.

The problem is the anti-vinculin is you. And you always have you. So the auto-antibody is the one that doesn't go down as much or over time. It takes a longer time, let's say it that way. So, that's the one we're trying to target to cure IBS.

[43:38] Is IBS an Autoimmune Disease?

Shivan Sarna: And when you're saying "autoimmunity," I know in the past we've had that specific question. Do you call it an autoimmune disease? And I know the

terminology can be so confusing if you hang your hat on something like that. HOw do you convey that for all of us who are thinking, "Wait a minute! Does that change the way I should be thinking about this?"

Dr. Mark Pimentel: Yeah, terminology is more political than it is anything else. There is politics to terminology.

The irritable bowel syndrome concept, if you think about it, *irritable bowel syndrome*, the word "syndrome" means that it has no understanding of cause. It's just a constellation of symptoms. So by having this test, IBS really is no longer a syndrome. It's a disease. But there has to be consensus change and so forth.

So, it's complicated. But yes, I would consider IBS an autoimmune disease if you have these antibodies. Absolutely!

[44:42] Updates on the SYN-010 Trial

Shivan Sarna: Allison, you want to chime in a question that we pre-talked about?

Dr. Mark Pimentel: You're on mute.

Shivan Sarna: Oh, you're muted.

Dr. Allison Siebecker: Hi! I'm unmuted.

Yeah, can you give us an update on what is happening with the methane-specific treatment you have been studying a while ago, SYN-010?

Dr. Mark Pimentel: So SYN-010, unfortunately… lovastatin is still the principal component. Lovastatin blocks the F420 enzyme in methane-producers. So if you

were to pour lovastatin, which is a cholesterol drug, on methane-producers, their methane goes down dramatically.

Now, trying to get that to the correct parts of the gut was the problem. The design of the product didn't quite do what it was supposed to do. So the trial was not so successful unfortunately. We always thank the patients for having participated. But it didn't quite work out the way we hoped. The patient's methane went down. It was a good thing for them. But it didn't always go down related to the drug. And so that was the challenge.

I hate going back to the drawing board. That was three years of work for all of us here. But we have to be intellectually honest. It didn't work. And we have to figure it out. So that's our challenge.

[46:10] SIBO vs IMO

Dr. Allison Siebecker: On that note, we've had a bunch of people who were getting confused with the new IMO terminology. And so I just wanted to ask you about that. And specifically, what seem to be coming up was people were thinking that it was a new disease and that we have no treatments for it. Can you just talk to that?

Dr. Mark Pimentel: Intestinal methanogen overgrowth is an overgrowth, but it's of those methanogens. We have treatments. I already showed you a double-blind study—rifaximin + neomycin. That works for IMO quite well.

Nothing is perfect. There are patients who still struggle. And we need to find better answers. But for a large majority of patients, the rifaximin and neomycin is quite successful. So we have treatments.

We just want to make sure that we're not calling everything "SIBO." We want to be scientifically and intellectually accurate on how we're labeling things. That's all!

Shivan Sarna: I just want to say to the community to not overthink that. It's like you said, I think you called it "different flavors." I love that part. That is a great way to look at it.

Sometimes, when we get into what I call "SIBO panic," we're just really being so literal that it distracts from the project at hand… which is to treat it. And there are treatments.

[47:37] Stomach Acid, GERD, PPI's & HCl Supplements

Shivan Sarna: Talk to us, if you would, about a very hot topic which is stomach acid, PPI use, et cetera. And if you could explain what a PPI is. Just help everybody who has GERD. They're sometimes taking HCl supplements, and they're getting helped; and other people are like, "Wait a minute! I thought that was making some of my SIBO/IMO worse according to Dr. Pimentel." So we just need clarify for everyone on that, if you would.

Dr. Mark Pimentel: Yeah, there's a lot to say about acid because a lot of you out there use acid in different ways or block it in different ways.

And so, many people are on acid blockers. If you have heartburn, you get on a PPI which is a proton pump inhibitor. It blocks acid being secreted into your stomach to help digest food. And so you stop the acid. The heartburn goes away.

But acid is one of the protective mechanisms for bacteria getting into your body. So if you have no acid, you have the chance that, if what you eat has bacteria, it gets past that stomach guardian acid, and it gets into the small intestine.

So, there is always this belief that, hey, if you take a PPI, and the acid is zero, you're going to get SIBO. And we did some breath test studies early on, and we said, "Hey, we're not seeing that. We're not seeing that at all."

And then, we did the REIMAGINE Study, and we looked at people who were on PPI and no PPI, absolutely no difference. What we did see is ***clostridium* goes down with PPI**.

Now, what does that mean? It means your nice, beautiful, normal *clostridium* which are protecting the *clostridium* neighborhood are gone! **That means *C. diff* can come in as an interloper**. And then, you get this *C. diff* colitis thing. That's well-established in PPI use.

On the flip side, people are taking acid—apple cider vinegar or other things. They say, "Oh yeah, more acid to kill more bacteria." But on the IMO side, methanogens love acid. They love hydrogen. Anywhere they can get hydrogen, they will produce methane.

So, if you put vinegar, take vinegar or acid as a supplement, it's possible that you're going to increase methane. How do I know this? I know this from the PPI story. **We saw people on PPI's had less methane**. So that means less acid in the gut, less fuel for methane.

What I don't want you to take away from that is take a PPI to make methane go down. That part, we're not quite sure if that's going to work in a prospective way. But we did think about adding PPI to lovastatin to help get the lovastatin to be more effective. And it's a work in progress.

Dr. Allison Siebecker: Now, on this PPI front, there are so many patients who feel that they got their SIBO after being on a PPI, just their sense of things, how they've put it together. Your studies show that we really can't make a causal connection.

Early studies had always listed PPI's as risk factors. I don't know, what do you have to say, especially to the people who feel that they got it from PPI's.

Dr. Mark Pimentel: I sort of glazed over one of the slides that I showed. But the question you need to ask yourself is: "Why are you on a PPI?" You obviously have a digestive disorder in order to need a PPI. And one of the digestive disorders that leads to reflux potentially is anything that causes pressure in the abdomen. SIBO does that. More gas, more pressure, more reflux potentially, right? So maybe you had SIBO all along, and now you're on a PPI. That's one explanation.

The other explanation is dyspepsia we now know is a post-infectious disorder too and is caused by SIBO. I showed you that with the Australian study. It included IBS and dyspepsia patients. And the treatment for dyspepsia is PPI—or they're commonly used.

So, it could be that we're mixing things up and not focusing on "Well, why did you have a digestive issue to begin with that you needed the PPI for?" Maybe it was SIBO all along. Maybe that all came from food poisoning also.

So, maybe I'm being confusing. But hopefully…

Dr. Allison Siebecker: Not at all…

Shivan Sarna: Wait! Tell us what dyspepsia is for somebody who does not know.

Dr. Mark Pimentel: Dyspepsia is you feel sort of that raw sensation in your stomach or you feel heartburn. That's another symptom of dyspepsia.

[52:28] Re-Test: Going From Bad to Worse After Treatment

Shivan Sarna: Can we just talk about hydrogen in general then? Occasionally, I see people saying, "I did my treatment. I did my breath test after the treatment to see how it went. And there's more gas now. What the heck?!" Did you see this a lot? How do you interpret that?

I know Dr. Siebecker and Dr. Steven Sandberg-Lewis have a name for it. What do you call it, Allison?

Dr. Allison Siebecker: *Pissed-Off Bacteria Syndrome* or *Pissed-Off Methanogen Syndrome* if it happens with methane. It was just very early on. We saw this, and we gave it a fun name.

Shivan Sarna: Sometimes, you just got to laugh.

Dr. Mark Pimentel: No… we see that! Okay, we see that with methane for example. You've got a methane-producer. And you know methane is eating four hydrogens to make one methane. You get rid of methane, all of a sudden, the hydrogen goes up because the wolves eating the rabbits are no longer there. So the rabbits are going up, and you're seeing all the hydrogen.

The same thing with hydrogen sulfide. You get rid of the hydrogen sulfide you didn't know was there because we didn't have hydrogen sulfide three years ago. And then, all of a sudden, the hydrogen goes up after antibiotics.

I've had patients say, "Oh, doc, my diarrhea is so much better." We did a breath test, and the hydrogen is higher than it was before. Well, that was hydrogen sulfide because now we have hydrogen sulfide, we're seeing that happening in real time.

So, it all speaks to you've got to do all three gases because, otherwise, you don't understand what you're seeing. And then, when you see the hydrogen sulfide go down, the hydrogen go up, you go, "Oh yeah, Mrs. Jones, this is what's happening." Now, you can see it on the breath test.

So, the right information helps you make the right explanation.

[54:14] Disruptor Taxa

Dr. Allison Siebecker: On that note, can I jump in? You were just talking about the three gases and the hydrogen sulfide. Of course, you've identified *F. varium*. But we're also anxiously waiting to hear if there's going to be any other bugs identified for hydrogen sulfide. When can we expect to learn about that?

Dr. Mark Pimentel: The good news about methane is there's only two characters that are of importance to methane. And of those two, 90%, it's *M. smithii*. It's a super simple story—not simple. It wasn't simple to find. But now that it's out there, it's simple.

Hydrogen sulfide, there's probably 10 or 20 organisms that can produce hydrogen sulfide. It doesn't mean that all of them are involved.

For example, many bugs produce hydrogen. But we now know the hydrogen characters that are causing trouble are *E. coli* and *klebsiella*. Many produce hydrogen sulfide. But we're finding two or three characters—that I can't tell you today—are producing hydrogen sulfide and are really the culprits here. You'll know soon. It's all coming up.

Dr. Allison Siebecker: Are some publications to be expected?

Dr. Mark Pimentel: Yes, already done and submitted.

Dr. Allison Siebecker: Oh fantastic!

And when you were talking about hydrogen earlier in your presentation, the *E. coli* and the *klebsiella,* you were talking about trying to find treatments, drugs, trying to get the drugs to the right location to handle the *E. coli* and *klebsiella.* Can you talk about that a little bit?

Dr. Mark Pimentel: I can't give you a lot of details because that's also coming out later this year. But what I can tell you is that we now know *E. coli* is hiding. It hides from the antibiotics, in particular, rifaximin. So, we think that by getting them, we get them down.

One of the interesting things—and this is something that we're looking to present—what we see after rifaximin is, you would expect, "Oh, you took an antibiotic, and your microbiome is all going, including *E. coli,*" but it's exactly the opposite. What we see is that the rifaximin kills the *E. coli* and *klebsiella*. And then, after the rifaximin is done, you see this beautiful growth of everything that was supposed to be there. And so that beautiful diagram comes back. By getting rid of the bullies, the school is healthier.

Dr. Allison Siebecker: That just makes me think of the article you put out in the fall which was fascinating about **disruptor taxa**. Really, that's what you're describing here. They just disrupt everything.

Dr. Mark Pimentel: Yeah, get rid of them, and everything just bounces back to a nice, health environment. Get rid of global warming, and the coral reefs will grow back again. Sorry!

Shivan Sarna: No, that's fine. Feel free, feel free…

That's so exciting! This is a message of hope. This is a message of resilience. And that is what we're so happy to be able to share. We salute you, Dr. Pimentel, for all of your hard work and your whole team. So please send our love and our best.

I'm not wrapping it up. I'm just saying… this is exciting times! It's so exciting. I'm just over the moon. And also, I think we need to remind ourselves of how incredible our bodies are, right?

Dr. Mark Pimentel: Yeah, absolutely. And the 22 people working back there…

Shivan Sarna: God bless them!

Dr. Mark Pimentel: There's 22 people. That's a lot of people. And so things go faster. So I'm really excited about our new space and the new people—many PhD's who are super smart. They're making me look smart. They're just fantastic. They're really, really brilliant people back there.

Shivan Sarna: On that note, if somebody wanted to make a non-profit donation, is that set up for the MAST Program for this?

Dr. Mark Pimentel: If you just go to my Twitter, there's—I'm not doing this program for that purpose, but you brought it up…

Shivan Sarna: I didn't know I was going to ask about that.

Dr. Mark Pimentel: We do have a link on my Twitter, @MarkPimentelMD. But no pressure to do anything like that…

Shivan Sarna: That is Shivan Sarna saying go afterwards and donate if you can please—even if it's a dollar. Imagine! That's just me. Obviously, I didn't talk about Dr. Pimentel about that beforehand. But it's so near and dear. It takes a village.

I was thinking about the 22 people and how we can have this incredible domino effect...

Dr. Mark Pimentel: We have an amazing group of small and larger donors that are just making an enormous difference. And that enables this. So we're always grateful for all the help we get. So thanks for the pitch.

Dr. Allison Siebecker: I have more questions.

Shivan Sarna: Yes, we have more questions. By the way, hold on, Allison. If anybody feels like, "Oh, my gosh! I do have to leave" or something, don't worry, we will be sending the recording out. We will be sending a professional searchable transcript out.

And also, every single time that Dr. Pimentel has come on and spoken with me, Dr. Siebecker, we have it all in one spot. And we're going to be sending you that link too for free. So you can just watch over time how things have changed. It's very, very exciting! Let's start with this one first though.

Dr. Siebecker, go ahead!

[59:41] Methane & Its Impact on the Vagus Nerve

Dr. Allison Siebecker: You had so many fascinating studies come out in recent times. One of them I think that was also from the fall—I'm not sure when—and it was about methane and heart rate, which was so fascinating, that it can show to decrease heart rate. And you discussed in there that basically methane can have an action on the parasympathetic nervous system and might be affecting the vagus nerve.

The vagus nerve is something so many of our audience are very interested in because they're thinking about its connection with the migrating motor complex. If this connection is there, if the vagus is inhibited, and that's leading to inhibited MMC, might that mean we really need to get rid of—or *normalize*, not *get rid of*—normalize the methane gas levels to have a positive effect on the vagus nerve?

I don't know. Just tell us anything from your study.

Dr. Mark Pimentel: We always knew methane was doing some provocative things. And of course, we know methane slows the gut down. That's what's doing it. The more methane you have, the more it affects what we call the smooth muscle of the gut. The smooth muscle is the automatic muscle. You don't have to focus on digestion. It's happening for you. The more methane you have, the more impaired that us.

I'm going to try and compare methane to anesthesia gasses. When you get put to sleep for an operation, they often use isoflurane, enflurane and halothane. *Methane, halothane* and *enflurane*, you can tell there's a pattern. They're called *hydrocarbons*.

Hydrocarbons have effects on the smooth muscle of the gut. So when you go under for your gallbladder surgery, your blood pressure changes and your heart rate changes. So we said, "Well, maybe methane is associated with that."

Well, guess what? You also fall asleep. That's what you do when you go under. Well, methane we think is also responsible for the brain fog that patients get when they have SIBO, especially those with methane. And we see more brain fog there.

So, it's a hydrocarbon. It gets everywhere. And it can have effects. But it slows the heart rate down. That's very clear from that paper… which was really, really interesting.

We sort of had a little spin-off of that. We saw actually patients with pacemakers have more methane than patients who didn't. We didn't put it in the paper because it was a small subset. But it's just very interesting.

Dr. Allison Siebecker: And can you comment any more on the relationship with the vagus nerve?

Dr. Mark Pimentel: So it's hard to test the vagus nerve. There are specific tests. What we did see is that if you do a pancreatic polypeptide test, it was more often abnormal.

Pancreatic polypeptide test, this is really gross, people. Pancreatic polypeptide is a peptide or a protein that's released by the pancreas when you are ready to eat. You're thinking about eating, it's already going up. You put food in your mouth, it goes much higher. When it gets into the stomach, the food, then it really goes up.

But the way we do the test is we measure in the blood the pancreatic polypeptide level just fasting. And then, after you take food, you chew it, and you spit it out. You don't eat it. You don't swallow it. And that wasn't going up in patients as well with patients with methane.

So, there were a number of things we're seeing with methane that suggests its vagus.

Dr. Allison Siebecker: So potentially, it's almost like you can get methanogen overgrowth because the MMC isn't working very well. But then, once you have it, you're really screwed because then it's potentially limiting the movement more?

Shivan Sarna: Right, that's exactly right. Let's talk about the SIBO story. The SIBO story is you got all those antibodies that are causing things to slow down. And that helps the SIBO stay.

In the case of methanogens, the methane is slowing everything down to keep the methane bugs staying. And so it's two sides of a coin. But the principle is... if you can slow it down, we can stay in this home. And harmony is not reached. We have to find the middle ground.

Shivan Sarna: Wow! That's a lot.

[64:03] Sourcing Rifaximin

Shivan Sarna: Do you have any tips for how patients can get rifaximin? I know that they have patient assistance programs. But any suggestions? A lot of practitioners are here. A lot of patients are facing very high cost for the drug?

Dr. Mark Pimentel: Look, what I've tried to show today is that IBS-D is SIBO and SIBO is IBS-D in a lot of overwhelming senses. So therefore, it's okay to say it's IBS-D. And it's approved for IBS-D. So that's the best way to get it.

Back in the day before it got approved, your insurance companies were saying, "Well, we want to make sure it's SIBO before we give you rifaximin" even though it wasn't approved for SIBO. Now, it's approved for IBS and they said, "Well, SIBO is not IBS." It's flipped! But it is IBS. So call it IBS because it is IBS.

I think that's the confusion. You want to stick with what it's approved for by the FDA which is IBS. So in a sense, you have ulcerative disease, but it's caused by H. pylori... it's ulcerative disease. So just call it ulcerative disease, that's what it is. And then you're more likely to get it approved by your insurance.

Shivan Sarna: So even if you have IBS-D, it's okay to call it IBS-C? Is that a suggestion you could make to your doctor?

Dr. Mark Pimentel: Well, the C is trickier. You're not lying and being deceptive when it comes to IBS-D and the SIBO relationship because they're one and the same.

Shivan Sarna: Thank you.

Dr. Mark Pimentel: When it comes to IBS-C, it gets a little trickier with the insurance companies if the insurance companies is being stubborn and saying, "Look, it's only approved for D. Why are you taking this?" and that kind of thing.

But what we often do is we send the insurance companies the double blind study and say, "Look, there's evidence that works." And usually, that does it, especially if your doctor's office is receptive to that and willing to go the extra mile.

Shivan Sarna: Yeah, thank you.

So, just to clarify for my friend, Michelle, who has IMO, and is very focused on this terminology thing—and I understand, Michelle—she's asking (and this is a question I was going to ask anyway, so don't anybody hate me because I can only ask so many questions): "Is IMO caused by food poisoning or just SIBO?" But you see, it's the same.

How can we answer that for people who have that question?

Dr. Mark Pimentel: Okay. The answer is that we don't see the antibodies elevated very often in C. Connecting food poisoning to constipation, that line is not straight. Connecting food poisoning to SIBO and D, it's a straight line.

So, I don't routinely measure the antibodies in C. So I would advise you not to do that. It just isn't cost-effective because you're not going to see it too often. That's the point I'm trying to make. It's not food poisoning there.

But the real question you're asking is: "Then what the heck is it?" I don't know. We don't know yet. Why does methane go up in some patients, and other people, it's nice and in a normal location? That's a mystery still to solve.

Shivan Sarna: Okay, great! And this double blind study that you just referred to, I'm going to get so many people emailing me asking which double blind study. We can just help them find it in PubMed. Which one are you talking about?

Dr. Mark Pimentel: I'm talking about in Digestive Diseases & Sciences. I believe it's 2012. I'm one of the authors on it if you search that way. And you're looking for *rifaximin* and *neomycin*, that study. It's a double blind study.

Shivan Sarna: Thank you.

And a couple of people are saying that they just had the doctor say IBS with no initial next to it. Their insurance company approved it along with the coupon from the manufacturer. So I just wanted to address that. I know it's a huge question.

[68:27] Breath Testing: Glucose, Lactulose & Fructose

Dr. Allison Siebecker: Mark, you and I were talking a little bit about the breath testing substrates because Shivan and I had just sent out an interview presentation we did with Dr. Hawrelak where he surprisingly found fructose did a very good job of identifying SIBO when done in the style of a longer test. Typically, fructose substrate tests weren't used for SIBO. But he did it with multiple tubes and a long time.

He found that actually glucose was not as good as he originally thought. Lactulose was good. And fructose was even better.

When I emailed you about it, I thought you had something very interesting to say which didn't surprise you. But what's hard is convincing people that a positive fructose test can be SIBO. So can you talk about that a little bit?

Dr. Mark Pimentel: Yeah, because there are multiple breath tests. What I mean is the breath test is the same, but the sugar is different.

For example, people do lactose breath tests to look for lactose intolerance. It's going to get a little convoluted but work with me. Lactose intolerance means you drink milk, you get bloated. That's lactose intolerance. It doesn't mean you don't absorb milk. It doesn't mean you don't digest lactose.

The way lactose intolerance works is the milk sugar which is hard for every human to digest more than glucose (glucose is super easy), it comes in right away. Lactose takes work. Everybody as an adult takes more work to digest lactose. So, you almost need your whole small intestine to absorb a glass of milk. That's everybody.

But imagine you have overgrowth. Now, that milk sugar isn't getting in so fast because it doesn't anyway. And you have bacteria there saying, "Oh, we'll take it first because you didn't get it," and now you have bloating and symptoms.

So, is that lactose intolerance? Well, sort of. You're having bloating after drinking milk. If you got rid of the overgrowth, you wouldn't have it. You'd absorb it perfectly.

So that's the problem with the lactose breath test. If you have bacterial overgrowth, you're going to be positive with lactose.

Fructose is the same thing. If you drank—I'm not picking on Snapple. But if you drank one Snapple, a regular Snapple, not the diet Snapple, or one Coca-Cola, you have enough fructose in there that it exceeds the capacity of most people's digestive tract for fructose. So if you have SIBO, you're going to have symptoms from it. If you don't have SIBO, you won't. And hence, the breath test will be positive with fructose if you have SIBO.

So, in the North American Consensus, we didn't call it fructose specifically, but we said "if you want to do lactose breath testing for lactose intolerance, you should first check for SIBO because if you have SIBO, it's going to be false positive."

The question is why is fructose even more provocative than lactulose? The reason for that is fructose is much easier for bacteria to digest. Lactulose is a synthetic sugar. And not all the bacteria know how to do it.

So, it may be better in some ways for picking up SIBO. But the problem is you don't know if you have fructose intolerance or a SIBO. Whereas with lactulose, humans don't digest it at all. So it's more clear.

So, we prefer lactulose over fructose. It was clear as mud, right?

Dr. Allison Siebecker: It was great! It's great. You basically have secondary lactose or fructose intolerance when you have SIBO very often, yeah. Thank you for talking about that because I know it's on people's minds since we just sent that out.

Shivan Sarna: And when you clear the SIBO, you see those intolerances improve, right?

Dr. Mark Pimentel: Often yes. So, if you clear SIBO, all of a sudden, people drink milk, or we do another lactose breath test, and it's perfectly normal. The problem is all that sugar getting down there, if you have that antibody and the gut's not moving well, it's just fuel for bringing the fire back. So we generally tell people to avoid lactose so that the SIBO doesn't come back quickly.

Dr. Allison Siebecker: On their post-treatment/SIBO prevention diet?

Dr. Mark Pimentel: Right!

Shivan Sarna: So therefore, the role of prokinetics is still very important for everybody?

Dr. Mark Pimentel: Yeah… prokinetics, we did one study where we checked how prokinetics worked. And they can delay it by two or three-fold depending on which prokinetic you use. After all, IBS and SIBO are a motility problem. Trying to keep the motility going is key.

I'd often use this analogy. If you ever watch those survival shows… they drink water from a rapid-flowing stream because that's clean. They don't drink it from the stagnant water. So the small bowel should be a nice, rapid, flowing stream. And that keeps it nice and clean.

[73:53] Can Parasites Cause SIBO?

Dr. Allison Siebecker: On that food poisoning thing, a question that so many people always have is we talk about pathogenic bacteria like *campylobacter* causing it. But people always wonder… can parasites cause it? Can parasites do the same thing?

Dr. Mark Pimentel: I found out a very cool thing! You know who has a ton of vinculin? *Giardia*. It's part of *giardia*. So the question—which hasn't been answered yet—can *giardia* cause anti-vinculin antibodies? I wonder yes because a lot of these parasites are more closely linked to our cells in the sense that they have those proteins.

What's amazing about vinculin is that it must be a super important protein because, no matter where you look, it's identical. If you go to us, if you go to parasites, if you go to whatever level, vinculin is vinculin. It's always the same. And so it's an important protein. And I guess campylobacter hijacked it.

Dr. Allison Siebecker: Campylobacter and the other bacteria.

And are there any other parasites that we know of that can lead to SIBO and IBS?

Dr. Mark Pimentel: If you look, *Trichinella spiralis* is a model of IBS that's been developed in Canada, another parasite, sort of a pig worm. There's a number of parasites that could. But they're so uncommon in the US that we won't have good tracking. It's a little difficult to show the associated. But the two that are well-known are *trichinella* and *giardia.*

Dr. Allison Siebecker: And *giardia* is not uncommon at all!

Dr. Mark Pimentel: No, it's not. Exactly, exactly.

[75:41] Can Viruses Cause SIBO?

Dr. Allison Siebecker: And what about viral. We know that food poisoning and acute gastroenteritis is so common for viruses. And that's the other thing people always wonder about.

Dr. Mark Pimentel: Yeah, there are publications that show that. But if you look at viruses, the chance of developing food poisoning is way, way lower. And even when you look at the four bad actors, *E. coli, salmonella, shigella* and *campylobacter*, a lot of pathogenic *E. coli* that cause food poisoning, not all of them has the CdtB toxin. So that's why if you get *E. coli*, you're less likely to get IBS than if you get *campylobacter* because they all have CtdB.

So, the ranking is *campylobacter* is the worst, *salmonella* is second, *shigella* is third, and *E. coli* is the least likely to develop IBS. And that's sort of how we see it.

[76:40] Alinia for SIBO/IMO & IBS

Shivan Sarna: What about Alinia for treatment of IBS, IMO, SIBO? Have you played around with that at all?

Dr. Mark Pimentel: I occasionally use it. You have to go with what works for the patient. Not every patient responds to rifaximin. I have used it occasionally. One of the challenges there, just maybe more of a challenge than even rifaximin, is it's not approved for that and it's even more expensive in some cases than rifaximin. So that's the challenge with Alinia.

But it's basically nitazoxanide. It's similar to Flagyl or metronidazole. We haven't found that metronidazole to be very effective in SIBO. It's maybe 25% effective compared to 40% to 60% with rifaximin. But not a lot of good studies there.

[77:34] Rifaximin

Shivan Sarna: Rifaximin, does it provide those long-term benefits that we're looking for or just that short-term relief? Should we expect if we do have the antibodies to, until we find the cure, just pulse it? Does that seem reasonable?

Dr. Mark Pimentel: The rifaximin is approved as a pulse. You take it. And if you relapse, you can take it again. And then, the third time. That's how it's approved.

But what we don't know yet is that when the vinculin antibodies are at their highest, the highest levels, those patients, rifaximin works but for a very short time because the motility is so badly damaged.

I can tell you… I see people at the mall, and they said, "You treated my SIBO three years ago. I'm still great. I feel fantastic." Those people, their antibodies aren't high at all. So it's a pleasure to see them. And I'm glad that they're a one-and-done.

Shivan Sarna: Yes.

Dr. Mark Pimentel: Yeah, there are one-and-done's.

Shivan Sarna: There are.

Shivan Sarna: And how does C. diff play a role in this? That's not a food poisoning potential cause, right?

Dr. Mark Pimentel: No.

Shivan Sarna: We've already established that.

And rifaximin doesn't lead to C. diff, right?

Dr. Mark Pimentel: Oh, rifaximin can kill C. diff. So it's actually been shown to be almost as effective as vancomycin for C. diff—which is the ultimate treatment short of fecal transplant. There's a couple of new drugs too. Vancomycin is one of the staples of C. diff treatment. And rifaximin works as well.

For some reason, the drug company didn't continue to pursue the C. diff indications. So it is what it is.

[79:27] Dr. Mark Pimentel's The Microbiome Connection

Dr. Allison Siebecker: We have so important to say as we end here. You have a book coming out! Please tell us.

Dr. Mark Pimentel: It comes out April 12th. People have been saying, "Do another book!" because there's so many updates. There's tons of updates. And so, we finally did another book, and it's coming out. We're hopeful it will help more people.

The problem is my clinic is so packed and we can't take new patients. So we have to figure out ways to help all the people that are out there—and the doctors. Technical enough doctors will find a lot of valuable information there. But it's like my lecture. I'm telling you, you have a sophisticated audience. Someone you may be patients, some of you may be practitioners. But I use the same slides. You can understand this.

It's complicated to get where we are. But now that we are where we are, it's not that complicated. And so hopefully the book will help a lot of people who maybe don't have a doctor that understands this or they can hand it to their doctor.

Dr. Allison Siebecker: What is the name? What is the name?

Dr. Mark Pimentel: The Microbiome Connection. It's coming out. If you look up "Pimentel" and "microbiome connection," you'll see it.

Dr. Allison Siebecker: We can get it on Amazon?

Dr. Mark Pimentel: Yeah, it's already ready for preorder. That's already live.

Shivan Sarna: And we've put a link up for it in the chat. I already ordered mine.

Dr. Mark Pimentel: IBS Awareness month... April! That's when we're coming out.

Shivan Sarna: I love it! Perfect timing!

Dr. Allison Siebecker: I'm so pleased. Congratulations!

Shivan Sarna: Congratulations!

Dr. Allison Siebecker: And congratulations on all of these amazing research.

Shivan Sarna: We have to let you go because you know I always am true to my word about your timing. Thank you so much guys. Chime into the chat with some love for Dr. Pimentel. Keep him in your thoughts and prayers along with his entire team. Dr. Pimentel, bless you! We'll have you back when the book is out to do some promo for it. I can't wait! Thanks! Send our best to everybody.

Dr. Mark Pimentel: Thank you. Great seeing you both. And great audience! Thank you.

Shivan Sarna: Thank you. Bye everybody.

Well, Allison and I will stay on for a second. We'll say bye to Dr. Pimentel.

Dr. Allison Siebecker: Bye Dr. Pimentel.

Shivan Sarna: Bye! So you guys can chime in and just send that love. Send that out in the universe. Sending all the good vibes. Bye doctor.

Dr. Mark Pimentel: Bye bye.

Shivan Sarna: Okay, see you!

Well, that was deeply rewarding, Allison.

Dr. Allison Siebecker: It's so great to hear the news. Again, so many tantalizing hints of what's coming out in the near future—treatments for hydrogen sulfide, they've

been testing the bugs that are causing hydrogen sulfide, treatments for hydrogen, getting drugs to the right location, the fact that hydrogen isn't feeding the methanogens, or sorry, E. coli isn't the bug making the hydrogen that's feeding into the methanogens in IMO, a lot of things I have not heard him talk about yet.

Shivan Sarna: Yeah, it's very exciting. Thanks for joining me, Allison. I really appreciate it. I always love your insights and enthusiasm and questions.

Yes, everyone is getting the recordings. And when you click on another link we're going to also provide you in the email, you'll be able to go back and see all of the things that we've done with Dr. Pimentel over five years. That's a long time. That's a long time. You'll see the progression.

But like I said, start with this one. Re-listen to this one. Go back and check the area, the links that we're going to send you tonight. Give us a few days to get the transcript done. I don't know if we're going to re-send the transcript. Just know that the link we're going to send you shortly will have the transcript added to it. It depends on a couple of things whether or not we'll send that second email.

But thank you very much. If you are in the Facebook Group, and you're not already on our email list, go to SIBOinfo.com and get on Dr. Siebecker's email list, and go to SIBOSOS.com and get on my email list so you don't miss a thing. We are cranking! We have so much cool stuff coming down the pipe to share with you so that you will be able to be that empowered patient, that empowered practitioner.

If you are interested in becoming a SIBO pro, Dr. Siebecker created a SIBO professional course called SIBO Pro Course. You can find that on her site and mine. And then, if you're a patient, you're wondering how to navigate all these, certainly join us in the SIBO Recovery Roadmap® Course. That is a great option as well. It's also on both sites.

Okay! Thanks Dr. Siebecker.

Dr. Allison Siebecker: Thank you so much. Bye everyone.

Shivan Sarna: Bye everyone. Big hugs!