Digestive Disease Week 2022 Update for SIBO, IMO & IBS

With Dr. Mark Pimentel, MD

Hosted by Dr. Allison Siebecker, ND, LAc & Shivan Sarna

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[02:09] Introductions

Shivan Sarna: Alright! Hi everyone. We will start officially in just a minute. But no harm in introducing you to our very special guest. Dr. Allison Siebecker is here from the world-famous SIBOinfo.com. Hi Allison!

Dr. Allison Siebecker: Hello!

Shivan Sarna: Hello! Dr. Siebecker is a world-renowned SIBO expert. She's working on her book right now. She has done the SIBO Pro Course for all those pros out there who need true SIBO training. She also co-created with me—it's her content—the SIBO Recovery Roadmap® Course for patients. And I just want to say welcome to all of you all who are in our courses. And if not, we'll see you at the other webinars and all that jazz!

And of course, Dr. Mark Pimentel is here. Dr. Pimentel is going to be sharing with us the information from the recent Digestive Disease Week. He's the author of this book which I highly recommend that you get ASAP. And he's a professor of medicine and gastroenterology at Geffen School of Medicine UCLA and associate professor of medicine at Cedars-Sinai, Los Angeles.

He's also the head of Pimentel Laboratory and the executive director of the Medically Associated Science & Technology Program at Cedars-Sinai in Los Angeles.

Dude, that is a mouthful!

Dr. Mark Pimentel: And that's actually just the beginning...

Shivan Sarna: It is... seriously... just a small shout piece, I'm so excited... this is my book, Healing SIBO. It just got published in Polish everybody. So we're getting the word out there. The mission continues. And I am going to have you start, Dr. Pimentel, because we are right on time. And we have so much to get to.

Dr. Mark Pimentel: It's so good to see you both. And wow! Welcome everybody. It's a large audience. I can see the number of participants growing as we get started here.

I'm really excited this time because I really think we're coming to the end of a big part of the chapter on this. And I know we'll have a lot to talk about as we continue to unfold these slides.

So, as always, I'm going to show my slides. But I'm going to show you the slides as I show them to scientists, but I'll explain them to you so that you understand them. Those of you who are practitioners, and those of you who are just looking for information, everybody should understand this clearly. So I'm sharing my screen… and you should see my slides! Is that correct?

Shivan Sarna: Yes, that is correct.

Dr. Mark Pimentel: Okay, perfect. Are you able to make them full… yeah, there you go!

Shivan Sarna: We're here to do is to learn from Dr. Pimentel today. Go for it!

Dr. Mark Pimentel: Alright! Well, thanks again.

Let me start with one thing. I mean, one of the things that I'll commonly get both on social media and questions from people is: "When are we going to get treatments? When can I get treatments?" And let me just tell you that we can chew gum and walk at the same time. And we are chewing gum and walking at the same time. But what you have to understand is SIBO of 2010 is not SIBO of 2022. And we have to continue to understand SIBO where it's located, how it's distributed in order to perfect the best treatments.

Having said that, we're already in progress with clinical trials of new products and new technologies for SIBO on the basis of research I'm presenting today.

The other thing I want to tell you is, whenever I present research today, it's because it's public information. But we also have research we've already done that has not yet been public information. So we're always about a year ahead of what I'm presenting here—which makes me even more excited because there are other things coming, but also to tell you that we're not behind. It's just that we can't talk about things that are not yet public information.

But stay tuned because there's going to be a hell of a lot more now that we have all of these stuff that you're going to hear today.

[06:35] The Pathophysiologic Sequence of IBS

Dr. Mark Pimentel: I always show this slide as the mechanism of IBS & SIBO. Now, I talk about IBS and SIBO together because we think that about 60% to 70% of irritable bowel syndrome is SIBO. And while SIBO can be caused by a lot of different things—anything that slows the gut down can cause SIBO like adhesions and other things—the biggest, the gorilla in the room, is the IBS category. And we think about 60% to 70% of SIBO is IBS. And we've made a lot of advances in this area.

And so, what we show here is the sequence that we proposed a few years back. But now, we have all the pieces in place to substantiate this sequence. And I'm going to show you those pieces finally. So this is sort of a capstone lecture. And to be honest, it's the first time I'm presenting it publicly like this because we just presented a lot of this really big data at DDW.

So food poisoning starts the process. "I was fine until I had food poisoning," which is acute gastroenteritis. So the bugs that do that are E. coli, campylobacter, shigella, salmonella—those typical organisms after eating tainted food.

And then, this toxin is common to these organisms. And it leads to autoimmunity to a protein called vinculin (which is a protein in you). And then, you get a reduction in special nerve cells which are ICC's which are important for the migrating motor complex, which is the "cleaning wave" of the small intestine. And when your small bowel doesn't clean, you get bacterial overgrowth. And I'm going to show you the proof by all these different methodologies.

And then, of course, we know rifaximin has been effective with irritable bowel syndrome. But let's go beyond that as we start to understand what's going on exactly.

[08:35] How Food Poisoning Cause SIBO & IBS

Dr. Mark Pimentel: So, what I'm going to talk about first is what is the proof that food poisoning causes IBS. And I'm going to show you the best data on this.

But the best clinical study is from the Mayo Clinic. This is from 2017 in the Journal of Gastroenterology which is our top GI journal. And what you can see is that food poisoning causes IBS… full stop.

So, these were studies where they looked at let's say there was an outbreak of salmonella from, for example, in Spain, there was an outbreak of salmonella on a particular religious holiday when they were eating these cream cakes. And then they followed them over time and found that they developed IBS. That's one example.

All of these are more than 20 examples. And then they pulled them together and said, "Well, if you get food poisoning, and you've never had IBS your whole life, you now have a 1 in 9 chance or 11% chance of developing IBS.

And for many of the people who transitioned from food poisoning to IBS, they had IBS indefinitely.

And so, that's the starting point of this whole story, is this food poisoning leading to IBS.

This is a very complicated study that we published because we don't know—so what people are saying is "Well, okay, food poisoning causes IBS. But if you have a thousand IBS patients in your clinic, how many of them had food poisoning?" They don't remember. It's 10 years of IBS. They don't remember the first two days of diarrhea from eating bad sushi. So, what we have to do is a mathematical model.

So, we did this. We took this data from the Centers for Disease Control on the rates or what we call the incidence of food poisoning in the United States. We said this. We said let's pretend nobody in the US, 300 million people, nobody has IBS today. And then, overlay that with the incidence of food poisoning in the US (because food poisoning is a reportable illness. The CDC has accurate data on food poisoning). And then, we know that 11% develop IBS, but some of them get better. And not everybody has IBS indefinitely.

And then, creating this math model, and then modeling it over a period of time, we reached what's called a steady state at about 10 years. And the steady state is 9% of the entire 300 million population of the US, using all the available data at the time, could have IBS from food poisoning. So that's two-thirds of all the IBS we know in the

US, hence the 60% to 70% we think that food poisoning and SIBO and all of the things I'm going to show you are likely related to food poisoning in the development of IBS.

So, this is an important study. There's a lot of assumptions when you do mathematical models because it's very difficult to do a 10-year entire US population study. It would cost a tremendous amount of money. It would be impractical.

So, what proof do we have that food poisoning causes bacterial overgrowth causes IBS? There's a lot of data here. And I'll take you through that.

The first is that… this is now back in 2008. This has been in the works for a long time in our lab. We said "Well, food poisoning, the most common cause of food poisoning in the United States is campylobacter. It's hard to work with. The lab had to have certain certifications because it's considered a significant pathogen or bacteria that can cause illness. And so, we have to learn how to handle it, so we don't get sick. When the animals are in their cages, you got to handle the cage material in a particular way. So, it's a very complicated process to handle this organism in an animal.

But we infected animals on the right. This is the placebo group on the left. And then we waited 3 months. So, the food poisoning had to be gone (acute). The campylobacter in the stool had to be gone, meaning they had the food poisoning, they recovered from the food poisoning, and now we wait 3 months (typical for IBS, about three months after the food poisoning is gone, the IBS creeps in).

And what we did was we looked at the stools of these animals, and then we looked to see if they had SIBO. And 27% of the rats who had food poisoning had SIBO.

Now, what we saw in humans was 11%, not 27%. But we gave a large quantity of campylobacter. So, this would not be the kind of food poisoning you get. This is a much more dramatic amount of food poisoning. So, we're increasing the gain on this. But 27% of the rats developed SIBO.

But more importantly, the C+ means they got campylobacter. The SIBO+ means now they have SIBO. And then we went back to what their stools were. And 85% of these animals who were exposed to campylobacter and now have SIBO have sort of a diarrhea-alternating pattern.

So, not only did the rats get SIBO, but the food poisoning helped them develop IBS which is this altered stool form.

The only point to make down here is the only thing found in humans with post-infectious IBS is increased of these spectral white cells in the rectum of humans. And so, we checked that in animals too. And lo, and behold, we got the same thing.

So, this 2008 paper was the starting point of trying to understand the irritable bowel syndrome and SIBO relationship. Once you have an animal model that mimics exactly what humans get, we can use that to study drugs. We can use that to study all the facets of how this happens. And that's what we've done since.

So, fast forward to 2022—I'm not skipping steps, but I'm going to show you this—this is a study that we published in collaboration with Takakura who's out in Michigan and Mark Riddle who's a world expert in food poisoning. And what this is is called the Bradford Hill Criteria. What the Bradford Hill criteria is meant to do is to study cause and effect. So, to meet the Bradford Hill criteria means cause and effect is essentially proven.

So, you have to look at all these criteria on the left—consistency, temporality, biological gradient, etc. etc. And I'm not going to go through all the details. But the evidence in 2022 is, absolutely, campylobacter specifically causes irritable bowel syndrome.

And many of the studies that prove this are ours, plus others from around the world who have done some good research, showing that this is a true statement, that campylobacter causes irritable bowel syndrome.

[16:02] The Mechanisms Behind Food Poisoning: Cytolethal Distending Toxin-B (CdtB) & Vinculin

Dr. Mark Pimentel: So now we talked a little bit about CdtB because that's the toxin from food poisoning, and all these organisms which are now faded can cause it. Let's talk about what does CdtB do, how does it manifest. So, we're going to try and go through the really deep science—and I'm not going to let it get above your

head—deep science on what CdtB does to your body, or a rat's body, and then how it does what it does to get you to the point where you develop SIBO.

So, I've already mentioned this two or three times. Look at how different shigella, salmonella, campylobacter and E. coli are. They're very different organisms even just from their appearance in pictures. And yet they all share this one toxin.

And there are very few bugs that have this toxin. But this toxin obviously gives these organisms that we call "pathogens"—meaning they cause disease—an advantage of some kind that, until now, we didn't quite understand (and we still have more to learn). But CdtB is part of the important toxins that these organisms use to try and do something to us to their advantage.

These are a lot of colorful images. But this is what's called immunofluorescent staining. We use antibodies. We put it on tissue. And then, under a special microscope using fluorescence, we can see where the antibody is going.

And what we found—this is back in 2015—is that when we take the antibody to CdtB, and we put it on tissue. It's binding to these circles here. And you can see this is a special stain for this type of cell that we've known forever. This stain works for this cell. And this is the CdtB antibody, so the antibody to CdtB. And you can see that it turns from green (which it's binding to that cell); and then this antibody, when we put them together, it's orange, meaning that our CdtB antibody is binding to the same cell as a stain that stains for this particular cell. This cell is the cell called an interstitial cell of Cajal that is important for keeping your cleaning wave going.

And so, the antibodies to CdtB are binding to the cells that are important. These are nerve cells that keep your cleaning wave going. And it also binds to other nerve cells. These are called ganglia. And the same sort of thing is happening.

So, when you get exposed to this toxin, the antibodies you form against this toxin are binding to you and the nerves of your gut. But we had to figure out how this was happening. And that's on the right side.

We've got the special enteric neuronal stem cells. And then we broke them apart to just get their contents. And then we did what's called a Western blot. And then, we

put the antibodies on this Western blot. And what the antibody to CdtB bound to was something in the cells of these nerves. And that protein was vinculin.

So, while I always talk about vinculin, what I don't talk about is how many years it took to figure out it was vinculin. And we're talking five to seven years to confirm this because, in science, one binding is not fact. You have to look at—and I subscribe to this philosophy—you've got to look at it five different ways, and it has to come out the same. It's sort of like taking a picture of an elephant from five different angles to get its three-dimensional structure. We have to prove it in five different angles. And we did.

And I'm not going to go through more details than this because it's going to get too complicated. But we did this in so many different ways to show that the antibodies to CdtB were then becoming autoimmune to the protein vinculin. And that was causing the change in the movements of the gut because of this effect on these specific nerves and nerves cells.

Shivan Sarna: Wait a second, Dr. Pimentel. I just want to acknowledge the work because you're not getting people applauding. But I want to stand up and cheer when you're saying this, how you've connected all of this together. I just want everyone to take a breath and absorb this progress that you've made. I mean it's incredible!

And I know you're just working away in the forest. And then, you go to these conferences and people respond and stuff. But we want to thank you so much for all of your work. And just absorb what he's saying, you guys… this is so huge!

Okay! Sorry. Thank you.

Dr. Allison Siebecker: And actually, I just want to say that I was following along paper after paper… painstaking! One after another. And then, eventually, the final summary paper, it was just like reading a serial novel. Incredible! incredible!

Dr. Mark Pimentel: Yeah, it's a lot of work to put the pieces together and the resources. And the NIH funds none of these! And this is remarkable because most of what I'm showing you, we applied for NIH grants and got zilch! The NIH funds mostly inflammatory bowel disease and other conditions. Those are important too. But IBS is

the biggest, biggest, biggest, and the most expensive condition that affects people of all ages. It doesn't get respect.

But now, it's getting respect. And I think this story is part of the respect that IBS is getting.

Okay… so thank you for your little break.

[22:12] Understanding the Vinculin Protein & the Vinculin Antibodies

Dr. Mark Pimentel: So now let's talk about that vinculin protein. This is the vinculin gene. Where is that particular—

What I didn't say is that vinculin comes in many forms in different cells, but only the 117—117 means the size of vinculin, that particular type of vinculin—is the one that the antibody binds to. And they are present.

See, a vinculin of a different type is in the heart and other smooth muscles. But the vinculin we're talking about is in the small intestine and colon and in the skin. This is important for another thing we're working on. It's beyond the scope of this lecture. But it's important for the nerves of the gut.

Okay. So, this is a cartoon. This is from this paper here. Now, this is a little complicated. But if you look here, this yellow sort of fadedness is your cell membrane. So, you're inside the cell here, you're outside the cell here. And what's happening is that vinculin is this green thing that is sort of like a motor at the end of these chains.

So, think of this like a rope. These are the ropes that keep your cell in its innate shape. And vinculin is at the end facilitating those ropes stretching out to grab onto the next cell.

So, let me show you what that looks like in our lab. So, these are cells. You can see they're reaching out trying to grab onto each other and attach., The red is vinculin. The green are those ropes that are called actin.

What I tell my patients is, “Think of it like this… the wiring in your house. If the wire is there, but it can't reach the switch for the lights to turn on, there’s no electricity. You can be this far, and it won't turn on. This far, it won’t turn on. This far, it won't turn on. They have to be touching.”

So, vinculin helps the wires stretch and grab onto the next cell—and this is very important for nerves to grab onto each other so that the circuit is complete. And that's what goes wrong.

So now let's talk about those cells, those little round cells that I told you earlier. Look what happens? I’m going to show you the top diagram here. You can see the arrows are pointing to the cells. This is normal—cell, cell, cell, cell, cell, cell. And what you can see is the little string, like the wire connecting all these cells—cells, cells, cells, cells. That’s normal.

If you got campylobacter, the cells are further apart and a little bit more goofy-looking. And this is what happens If you had campylobacter and you have SIBO. It’s one cell here poorly stained… and then nothing—maybe one here and then nothing.

So, you can see… these cells were counted blindly, and that the lowest number of cells was always in the campylobacter and the SIBO-positive animals. So, these cells are decreased in number. And I’ll show you what the implications for that are. And that will be in this section here.

[25:36] How Gut Nerve Damage Lead to SIBO

Dr. Mark Pimentel: So now we know what the CdtB does, how it creates anti-vinculin. And then, it’s reducing these important cells that are important for the migrating motor complex. So, how does this lead to SIBO?

So, this is a study way back in 2002—this is our paper—where we showed for the first time healthy people and IBS patients with SIBO the migrating motor complexes. And you can see it’s dramatically decreased in patients with IBS who have SIBO. And then, also the migrating motor complex, which is this contraction to clean your gut, is also abbreviated. So, it's not only that it doesn't occur, but that even the ones that do occur are kind of incomplete—if you want to put it that way.

But what I'll tell you is that half of the patients in this group never had any that we could see. So that's what this says. Fifty percent of IBS subjects with SIBO had no MMC during the reporting period. So MMC's are the consequence of all of this phenomenon.

I show this paper because I want to give credit to Vantrappen who actually didn't discover the cleaning waves—that was Dr. Shashevsky from the May Clinic. But what Dr. Vantrappen said is these waves lead to overgrowth if you don't have them. This was a seminal paper from 1977. And so, all these pieces start to come together as to some of these historical works that didn't quite know the consequences of all of this or how this all fit together. But he certainly deserves credit for their discoveries before where we are.

So now let's take it in a different way. So now we know CdtB and anti-vinculin form. But how does that link to SIBO and or treatment?

So, we said, "Well, if CdtB is the ultimate cause of IBS, then why do we need to give campylobacter? Let's just give CdtB." So, we did this study where we gave CdtB as a vaccine to animals. And the vaccine was given a second time three weeks later—just like your CoVID, you get the first shot, then three weeks later, you get the second shot. And then, you see what happens. And that's what we did here. So, all these animals got Cdtb.

But the remarkable thing is the CdtB went into their muscle, in their arm or their leg, not in their gut. But what happens in the gut is amazing. So what we saw was they got anti-CdtB antibodies. They didn't have any before because they've never seen this toxin. Now, all of a sudden, of course, they have the toxin. But then they also had an elevation of the vinculin antibodies. So, by just giving CdtB, we made them have autoimmunity to vinculin. And that is a pretty incredible finding.

But more importantly—and I want you to focus on this graph on the right—the rats that got the CdtB inoculation got SIBO in their duodenum and their ilium (the Ilium is the last part of the small intestine, the duodenum is the first part of the small intestine). Basically, the small intestine, the bacterial count went up.

So, we started to postulate that this is how things happen. You get CdtB exposure, you form a bunch of antibodies. You don't like CdtB at all. You don't know it. You don't like it. You don't like this part. You don't like this part. You don't like this part. So you form a lot more antibodies to CdtB after infection.

But one of these antibodies looks a lot like vinculin or a section of vinculin. And now w we know this sequence—and we know this sequence which we can't talk about yet. But it will be very important for future prevention, vaccination for people who travel and other things that we're also working on. We can prevent IBS.

Shivan Sarna: Whoa! That's exciting. Hello?! You can prevent IBS. Does that mean you can prevent food poisoning?

Dr. Mark Pimentel: Yes, that's possible too. But even if you get food poison, it'll be milder, and we hope never create IBS in patients.

So, that is a 5-year goal. Stay tuned for more of that.

Okay. So now this was presented at DDW. This is going to get, again, very deep, very complicated with this. But this is public information. And this is some of our team members: Dr. Leite, he's one of our project scientists. He really spearheaded some of the analysis here and the research with us. So, this is really interesting.

So, we did the study with the CdtB again. But we wanted to take this to a new level with larger numbers to really figure out what exactly is going on with the microbiome now.

We know they get SIBO. But what kind of SIBO? Where is it? How is it? How is it factoring?

And again, same as the previous experiment, this is the control group, this is the injected group with CdtB. Of course, their antibodies go way up. Their stool wet weight goes up. Now, if you think going from about 61 to 63 is not a large jump… it's huge for humans. It's 2% more water in your gut. Remember, 2% of 8 liters is a lot of water. So this is an incredible jump in water weight. And the amount of CdtB antibody was proportional to the amount of increasing water weight. So, the rats, the more they reacted to CdtB, the more wet their stool was.

Now, I'm showing a complicated cytokine panel. These are inflammation that's happening in the body of the animal. This cytokine was changed, this one, this one, this one. You don't need to know the cytokines.

Here's what we did next. We said, "Let's pretend we put blinders on. We had no idea we gave them the toxin. We have no idea. Let's just take these cytokines and say, 'if this happened in a normal person or animal, what would be…'"—and there's a software where you just put the cytokines in, and it tells you what would have been guessed to have happened to that animal in order to get these cytokines the way they are. So, it's called a predictive pathway.

And I know it's complicated. Forget about what's in the middle. I'm going to point to what's important.

So, the upstream, what they're saying is the thing that could cause these cytokines to be the way they are is lipopolysaccharides (which is a protein in the bacteria that are typical of SIBO).

Secondly, what these cytokines would have predicted is autoimmunity (which we already know is happening). And what these cytokines would have predicted is diarrhea (which we already showed).

So, even not measuring diarrhea, not measuring the vinculin antibodies, not measuring the SIBO, just that change in your inflammation predicts exactly IBS and SIBO. And so, it's just internal validation of all of these factors.

We then sequence the animals in the duodenum, the ilium, the cecum, and the stool (the cecum is the first part of the colon as the small bowel enters). And all the remarkable things happen in the small bowel. You can see the control, big change; control, big change; small changes here. So, it's not happening in the colon. This is not happening in the colon. This is happening in the small intestine. So, we wanted to know what the big changes are.

So, we know SIBO. I showed you this—two different ways, two different studies. But what is the SIBO?

And so, the animals that got this toxin, they went in three different directions after the toxins.

So orange is where the bacteria—it's sort of a summary of their microbiome. The normal are orange. So, look at the orange cluster here. So, a group of rats who got CdtB stayed in the orange area. That's the green.

But then the rest of the rats went in two different directions. One direction was a lot more E. coli. Another direction was a lot of this organism. Desulfovibrio produces hydrogen sulfide. E. coli reduces hydrogen. This is going to become very important when we get the breath testing. I know you know about hydrogen, methane, and hydrogen sulfide.

But look what we're finding in the rats. It's exactly the same thing. The rats on the diarrhea side are going in two bad microbiome directions—E. coli or the desulfovibrio direction. And that's really important because that's what's happening in IBS. The IBS-D patient has two different IBS-D's. One is a hydrogen type of IBS-D. And another is a hydrogen sulfide IBS-D as I'll show you later. But we're seeing the same thing in the animal model—which is very reassuring that we're on the right track.

[35:25] CdtB & Vinculin Markers for Diagnosing Post-Infectious IBS

Dr. Mark Pimentel: So, what about measuring these toxins and these antibodies in humans? And how does that help us?

Well, this is the second generation test. And we got to use the second generation test because it's been improved so much from previous versions. It really is the gold standard for this testing now. And this is the IBS-Smart™ test because it accurately—

The problem with these proteins is they're unstable. And we figured out how to stabilize where the antibody combined. And this is really, really important to get these numbers.

But here it is. If you measure anti-CdtB in IBS, you can discriminate from Crohn's, ulcerative colitis and other IBD. Same thing with anti-vinculin, you can even more

clearly discriminate and be able to say a person has irritable bowel syndrome, and this was why it happened, because of food poisoning. So now we're confident in that.

And look what happens if you have both antibodies positive even if it's just one. The post-test probability of IBS is up to 98%. So, people are going to say, "Well, 98%, 89%..." Medical certainty is 80%. So, anything over 80% is considered medical certainty. So, we're in medical certainty if either of these test markers are positive, or both are positive. And the positive predictive value is over 95%. So that's really important.

People focus on sensitivity. So, sensitivity is low on this test. It's not low. Remember, I'm testing in this study—it's not a hundred patients, but just to give you an example, one hundred people, if they did the test, if you combine the two, it would be about 56%. But 43% would be positive for CdtB, 52% would be positive for vinculin. Some would have both. But it shouldn't be higher than 56% to 60% because only 56% to 60% of IBS is due to food poisoning. So it's right in the right spot.

So, don't focus here because this is actually correct. If I knew who had food poisoning, this could be a 100%. I don't know. So, focus on the specificity and the medical certainty that you get with this test.

Alright! So, we published this this year which really kind of shows you the story in cartoons of what I've been telling you this whole time. You've got beautiful organisms here. Look at all the different colors, different shapes, different sizes. That's all normal. That's all okay.

These are the special round circle cells I told you before. This is the ganglia that I showed you before, and then the muscle layers of the gut.

And then you get campylobacter, this green character that's now taken over here. You get the CdtB toxin entering your body. You then first form anti-CdtB antibodies. So here they are trying to get rid of the toxin.

So, there are patients who have IBS who only have CdtB antibodies. But they may eventually develop anti-vinculin or not. If they tend to have autoimmune disease, they're more likely to develop it. But the anti-vinculin doesn't happen until much later, three months after the food poisoning. So, you can be positive for one, or the other, or both... and it's still post-infectious IBS. So that's the estimation there.

And then, when the anti-vinculin rises as time goes on, you can see the characters here. These are now E. coli and klebsiella which we'll talk about.

[39:08] Gas Micro Typing: Hydrogen, Hydrogen Sulfide & Methane

Dr. Mark Pimentel: Now, let's go to the meat which is... breath testing culture, how do I apply this? How do I treat this? And so, i'm going to now go to the meat of what you can do today and what's coming.

So, this is a meta-analysis of breath testing. Breath testing should not be controversial because this study from Shaw (which is a study from Australia) looked at all the breath testing studies, and absolutely, without a shadow of doubt, breath testing is more likely to be abnormal in IBS to suggest SIBO than in healthy controls. And that's a full stop now.

And now we think 49% of IBS test positive on lactulose. Now, it varies from center to center, so it's a little bit of a scatter plot, because some centers don't think of IBS as a microbiological condition. They get referred to in a different pattern. It just depends on what center. But on average, you're talking about half the patients should be positive.

So, we now understand that there are three gases, not just hydrogen and methane. There's hydrogen producers, then there's hydrogen sulfide producers which eat up the hydrogen to make hydrogen sulfide. So, he your flat line breath tests aren't normal. They're hydrogen sulfide likely. And that needs to be checked.

And then, there are methane producers that eat four hydrogens to make one methane. And that's associated with constipation. The hydrogen sulfide is associated with diarrhea. And so, you have to measure all three gases.

Now, what we thought of until this year is that E. coli and klebsiella were the hydrogen producers of SIBO—and they are! But they're not the ones that are helping methane. So, the story has changed this fall a few weeks ago when we presented at the DDW. And I'll take you through that.

Small bowel culture shows the same thing. More SIBO in IBS versus healthy controls. And this is the case from a study all the way back in 2007, culturing the small intestine. We were part of the study with a group in Greece. And this is our 60% number. So, this is a really important study because this, once and for all, gives us a seat to sit on. Sixty percent of IBS has SIBO. Diarrhea IBS, 60% percent have SIBO by culture—not by breath test, but by culture. So, this is the gold standard.

It wasn't until 2015 that we started to understand E. coli and klebsiella are the two bad characters. So E. coli is here, klebsiella is here. And you say, "Well, that's not a big rise," but each number here is 10 times more. It's a log10 scale. So, there's 10 times more E. coli and klebsiella in IBS-D than in healthy people. So, that's not good.

One final study on culture that just came out in 2020, again, from the Shaw group in Australia, they looked at functional GI disorders (which is the group that is composed mostly of IBS, but some function dyspepsia patients). Look at that compared to controls, compared to Crohn's and ulcerative colitis… it's very clear that there's too many bacteria in the small bowel for IBS.

So now I want to introduce the ReImagine study. The ReImagine study is our flagship study. We started this now four years ago. We're trying to get now to 700 patients before the end of the year in this trial. It's the largest database of small bowel juice collected from patients who are just undergoing a scope from above.

We can't be doing it through colonoscopy because the colonoscopy washes things out. We don't want a washed out small bowel. We want to see what your small bowel looks like in its native state. And we're studying all these diseases, but we're going to talk mostly about SIBO.

The ReImagine study gave us the first beautiful look at SIBO in its detail. And it's similar to what I said—E coli and klebsiella. And I'll show you that.

This is a sunburst diagram that in the middle is bacteria, and then you break it down to the categories until you get to the genus and the species. And essentially, what you can see here is… this is klebsiella, this is E. coli in the SIBO. Look at the healthy people with no SIBO. Klebsiella is this tiny, little sliver here, and E. coli is this tiny little square here.

So, imagine that nearly 40% of all the bacteria in your duodenum in your small bowel is just two characters taking over like weeds in the garden. And I have some slides which I removed for the sake of trying to keep things under control for time that show how these two bugs basically destroy the rest. They're squishing everybody else down. They're taking over and forcing the others out (the healthy ones, I mean).

But this is an important slide. And I'm going to spend a few seconds on this because people talk, "glucose, glucose, glucose." And it's a little frustrating for me at this point now because I've heard the glucose story over and over again. And then, there were conversations at DDW saying, "Well, we recommend glucose." On what basis? Where are the studies? There are so many studies on lactulose, but there's hardly any on glucose… but people are saying glucose.

This study is from the Relmagine, patients who had lactulose breath tests. We compared the lactulose breath test to culture. And it's good. And we compared it to sequencing, and it correlates with the E. coli and klebsiella (which are gamma proteobacteria).

But not just that, the lactulose breath test, the 20 rise at 90 (which is the cutoff for a positive test) correlates with the upregulation of hydrogen enzyme pathways in the bacteria that are present in the duodenum. So, the hydrogen mechanisms, the machinery to make hydrogen, is increased in the small bowel of a patient with a positive breath test on lactulose. There's nothing like this on glucose. There's no data like this on glucose. The data for lactulose are overwhelming.

I'm not saying you shouldn't do glucose. But what you have to understand is glucose is often negative. And then, you do lactulose, and you get a positive test. The validity of all the things I'm going to show you are based on lactulose.

The other thing that critics have said is, "Well, we used to say 105 or greater than 100,000 bacteria in the gut, is SIBO." That's not true either. And we published an initial paper reviewing healthy people. No healthy person is more than 103—which is a thousand bacteria.

So, in our sequencing analysis from the small bowel. We showed that everything looks like this up until you get to a 1000 bacteria per milliliter, up until you get that

cut-off. And then all hell breaks loose. So, 103 or 1,000 bacteria per milliliter is the tipping point for the small bowel to become SIBO. This has been proven now.

So, now let's talk a little bit about intestinal methanogen overgrowth. I know that was part of what people wanted to converse about. You get this hydrogen production. We now know the bug, Methanobrevibacter smithii in the colon, and the small bowel, and it converts the hydrogen to methane. And that methane is proportional—so more methane, more constipation and bloating.

It also lowers your heart rate, the methane. So, the higher methane, the lower the heart rate. This is a new finding we have. And there are some anti-inflammatory effects, which I'm not going to get into here. But we're understanding M. smithii or this bug that produces methane more clearly.

New data from DDW… so remember, we changed this. It used to be SIBO with methane, and then it became intestinal methanogen overgrowth because methanogens don't just live in the small bowel.

Well, interesting… we used the ReImagine study to look at all the methanogens that are known to colonize humans. And there's a couple things you'll notice. Methanobrevibacter, which is the one that produces methane we believe in the IMO, intestinal methanogen overgrowth, in the small bowel, 14 out of 14 people had it; only 5 out of 14 had it in stool. So yes, the small bowel is where it's most present. But it is also present in stool. And then, there are other characters that produce methane at a lower proportion.

But the point is this organism is everywhere. Methanobrevibacter is in the duodenum, in the jejunum, in the ilium and in stool. So, it is intestinal methanogen overgrowth, not SIBO. It's not just in the small intestine.

So, this is the first study—you're seeing this first—the first study ever to look at the entire gut and look for these methanogens and how they're distributed through the intestinal track.

You say, "Well, okay, great. We already knew this." But we didn't for the purpose of developing drugs. Drugs have to be delivered where the characters are. And so, understanding the characters helps us develop the next level of drugs (which I told

you, we're about a year ahead of this data. So use your imagination. We're trying to develop things based on this work).

And the other gas is the hydrogen sulfide. So hydrogen produced by organisms like E. coli are used by bacteria to produce hydrogen sulfide. And hydrogen sulfide causes diarrhea urgency and pain which is the IBS-D in the gut.

So, for the first time, we can now measure hydrogen sulfide, hydrogen, and methane on a breath test that you can do at home. But this was not easy. Again, what we said earlier, Shivan, it takes years and years to go from the idea, to be able to validate something that can work effectively and correctly. You can't transport hydrogen sulfide easily. You have to get a bag with a large quantity of a gas (because the sensors need more gas) that is rated and capable of storing all of these gases without them decomposing. Hydrogen sulfide decomposes very easily. It's highly reactive.

And then, the sensors have to be oriented in a particular fashion, so all three gases can be measured from the same breath. And then, we have to establish a clinical cut-off using the bag, using the kit, using the machine that was developed, and all of that. So, all of that took a lot of time.

But what we can see is the hydrogen is exactly like other hydrogen breath tests, the methane is exactly like other methane breath tests—although the sensors in here are more accurate to a narrower arrange.

But here's our first results, taking patients with diarrhea—not necessarily IBS, but diarrhea patients. And so, the initial cutoff looked like 5. But now that we have IBS-D, the cut-off at this moment is 3. And that may change as we continue to get more data.

But without a doubt, the more hydrogen sulfide, the more severe your diarrhea is. And so, we know this is sort of starting to look like a cause and effect relationship.

[51:36] Treatment Summary

Dr. Mark Pimentel: So, how do we treat all of this? You probably know this study. This is from the New England Journal of Medicine. Rifaximin—this is a rifaximin study—it made everything better. And it made it better for up to 3 months.

The FDA approved rifaximin as an antibiotic for the treatment of irritable bowel syndrome because IBS is a microbiome condition. And that was an important pivot point in 2011. It took about 10 years to get to this FDA verdict.

But what we then learn is that, if you did nothing, no breath test, rifaximin would have an effectiveness of about 44% if you took a hundred consecutive IBS patients with diarrhea. If you had a negative breath test to start with, 25% would be would be successfully treated. But if the breath test was positive, 56% higher. So that's higher. And then, if the breath test became normal because the rifaximin worked, 76% met this very difficult FDA endpoint.

So, you can see that knowing that you have the alteration in the microbiome or SIBO really helps you with IBS.

For methane, we showed in this double blind study that neomycin, by itself, isn't very good. We also showed that rifaximin by itself isn't very good. But when we combined the two, they really have a better effect on making that constipation score go down in the methane patients. And if you get rid of methane, that's the patient that did the best in this in this trial.

Finally, we are again a year ahead of what you are seeing here today. We are working on hydrogen sulfide right now with the therapy in clinical trials. We are doing these things. But here's what we do now because of this study from 1998. Michael Levitt was a tremendous figure in gut microbiology really in the 1970s, ‘80s and ‘90s. You may know his son who wrote Freakinomics, a little tidbit. So, basically, bismuth markedly decreases hydrogen sulfide. And so we used this study as leverage for treating.

[54:10] The Microbiome: IBS-C vs. IBS-D

Dr. Mark Pimentel: Now, the final piece, this is the study we presented at DDW. This is really the most important piece of data that we have so far because it really ties

home everything that I've said, but it also ties home the microbiome, we have to understand and continue to understand the details so we can improve our therapies.

So, we took patients who were in a double blind study for IBS-D. These are perfect D patients. You can't be in a clinical trial for IBS-D under FDA without being perfect. And we took another study of IBS-C. It's the similar type of scenario, perfect IBS-C patients. Some of these, 53%, were methane-positive; some were not. And then, these of course are very similar in their demographics.

We did breath tests in all of these patients. You can see that, in the IBS-C with methane, obviously, they had methane. So methane was elevated. But the D patients did not have methane. And the IBS-C without methane did not have methane of course.

So, this is interesting… when you look at hydrogen, look at the threshold, remember, 90 is more than 20. It's above 20. And it's also statistically significant. So IBS-D patients produce hydrogen-positive breath tests. The IBS-C, because they're producing methane, they don't reach that threshold as often. So you can see they're down here.

Hydrogen sulfide… hydrogen sulfide is higher in IBS-D versus IBS-C. I've shown you some of that. But this is a very important study from very clearly defined humans with IBS, that hydrogen sulfide is on the D side.

Now, let's look at the microbiome. I'm not going to go through this slide. What I'm going to go through is say that, if you have methane, your microbiome is completely different than if you have IBS with diarrhea. So, the IBS constipators with methane are here. The IBS diarrhea are here. They're very different in these two sort of ways of looking at the entire microbiome of these humans as a group.

First off, we knew this before, but again, it's showing exactly the same thing. M. smithii, Methanobrevibacter smithii, that's the bad actor in IBS-C. It doesn't matter what time of the breath test this bug correlated. This is positive correlations with the breath test values and negatively correlated with hydrogen. So, the higher the M. smithii, the lower the hydrogen was because M. smithii is eating hydrogen.

Now, this is going to get deeply complicated, but I'm going to make it very simple for you. Remember, when methane produces methane, it needs hydrogen. But it's not getting hydrogen from E. coli and klebsiella, those two characters. Where it's getting hydrogen, now we know as of this DDW, is it's getting it from these two characters, Christensenellaceae and Ruminococcaceae. You do not need to remember their names. But suffice it to say that we can't treat E. coli and Klebsiella in IBS-C with Methanobrevibacter or methane because these are the guys that are helping.

And so, let's go in more detail here. The methane organisms correlated with methane levels. These two characters that provide the hydrogen correlated with methane levels because they need to make the hydrogen to make the methane. And also, they correlated with this higher diversity which I showed you earlier.

So, IBS-D side though had more of these two categories of bugs, Fusobacterium and Desulfovibrio that produce hydrogen sulfide. So, in humans with IBS-D, hydrogen sulfide was increased. And these are the bugs that did it.

I'm going to skip over this. But what I'm going to say here is that E. coli and Klebsiella, which is in this category, is what's giving the hydrogen to that hydrogen sulfide-producing bacteria. And there's a negative correlation with all these.

So, the hydrogen sulfide goes up, methane goes down; methane goes up, hydrogen sulfide goes down. This is what this is showing. This is going down, this is going up. So on the D patients, this is going up and hydrogen sulfide is going up, but these are going down. So it's a yin and yang. So you're either in the middle (which is normal), or you're pulling this way to make methane, or you're pulling this way to make hydrogen sulfide to cause diarrhea.

I'm not going to get into this because it's a bit complicated. But really, what I want to say here is we then looked at what's being produced in the gut using chemical analyses, or the analyses of the microbiome. And in the constipated patients, the IMO patients, methane is being produced—methanol, methylamine. And this factor, which is the most important factor for making methane, is elevated.

On the IBS-D side, it's all about making hydrogen sulfide.

So, this is the cartoon that sort of shows things. You've got hydrogen-producing overgrowth, you've got hydrogen sulfide-producing overgrowth, and then you've got intestinal methanogen overgrowth with production of methane. These are the bugs that are friends and helpers of this bug to make methane. The E. coli and Klebsiella are the bugs that help make hydrogen sulfide with these bugs. We now know the whole story of how the microbiome is interacting, the whole story in 2020.

So, back to this, this is how it works. So, you make hydrogen. You make it with E. coli and Klebsiella, but not for this. But the hydrogen is being used to make hydrogen sulfide. And that gives you diarrhea. Methane, it gives you constipation. And that's how it works.

[60:58] Testing & Treatment Protocols

Dr. Mark Pimentel: So, this is the whole story of what we know for the cause of food poisoning to develop irritable bowel syndrome. I've gone through each of these steps. I've broken them down for you in fine detail. But how do we use these tests?

And so, I really think in 2022, this is what we do in all of our patients now. So, it really should be sort of standard. And that is… you could just simply give rifaximin with that 44% benefit if you have sort of chronic diarrhea sounds like IBS, but I don't. I do the antibody because the antibody tells me how bad that patient is going to be. It gives the patient the answer that that is what caused the IBS, food poisoning.

We do the 3-gas breath tests now. We don't do the 2-gas anymore because the two gas breath tests don't give us enough information.

If the antibodies are positive, you know now, with more than 90% certainty, that food poisoning caused this for them. So, you have to counsel about travel. You have to tell them these antibodies can go higher if you get food poisoning again. Be very careful because it's going to be harder to treat your IBS if these antibodies rise. So, you must know what these antibodies are.

If this is negative and the breath test is negative, you beat it. You better be looking for something else. We have lots of examples now where we have done these two tests

as a starting point, and they're both negative, and then we move on, and we find stuff—Crohn's disease, microscopic colitis, other things.

But if your 3-gas breath test is positive for hydrogen, you get rifaximin. If it is positive for hydrogen sulfide, our clinic uses rifaximin + bismuth. This is how I do it. We're waiting for clinical trials that are coming, as I mentioned, to guide us in even better ways to treat hydrogen sulfide. You'll see that in the coming months maybe within the next year.

For mixed patterns, I do the same thing.

On the chronic constipation side, if you're just looking for methane, you could do the 2-gas breath test (but I'm just doing 3-gas breath tests all across the board now). So, for methane positive, you treat with rifaximin and neomycin. For methane negative, look for other things causing constipation. So, this is how we do it.

You could substitute the neomycin for metronidazole if you don't like neomycin or if you can't get neomycin.

[63:21] Takeaway

Dr. Mark Pimentel: In conclusion (this is my final slide)…

IBS is commonly a small bowel microbiome disease. We now know this for a fact.

SIBO, it's an important contributor to irritable bowel syndrome. As you see, the most important organisms for SIBO are E. coli and Klebsiella in the small bowel.

Methane is associated with constipation. And we now know the bugs that are helping to feed the methane.

Hydrogen sulfide is key to understanding SIBO more completely and is associated with diarrhea. So, if you don't measure all three, you're missing out on some of the important pieces of what to do here.

Reducing methane is important.

Measuring CdtB and vinculin are important to understanding that food poisoning caused it for this patient.

And because of this biomarker, number eight, you can see that IBS is really an organic disease. It is caused by these antibodies we believe now. It's important to get these measurements in order to educate the patient, but also educate yourself on how to manage these patients because it will be more difficult the higher these antibodies are.

We're developing new targets now. Now, this is as complete as we think we need to really move on treatments. You can see that, if we did develop treatments two years ago, we may have had an incomplete understanding of what to do. But now, the story is much more complete.

So, thank you. Sorry. I hope it wasn't too complicated but this is like an epic tour de force of everything.

[64:55] Q&A

Shivan Sarna: It's amazing! That was incredibly comprehensive... incredibly! Thank you so much.

Before we even lose any thought pattern, I just want to ask you, does the microbiome reset itself after these bad players are dropped through treatment?

Dr. Mark Pimentel: Yeah, I have so much data. I can't share everything in one talk. It's just too much. We have a beautiful study where we looked at the small bowel microbiome in a SIBO patient before and after rifaximin. And the rifaximin was effective, the patient was better.

Maybe this is a bad analogy. But it's sort of like if a gang comes into a small town, it kind of takes over like the old West. Then everybody either leaves or hides. Once you get the gang out, everybody comes back to their homes, and everything goes back in order. That's exactly what they saw. The diversity goes up, the diversity of the microbiome becomes more normal. And it's a beautiful thing to see on these sequencing studies.

So, it really is. You get rid of the bullies and the population returns to normal.

Shivan Sarna: About how long does that usually take, Doctor?

Dr. Mark Pimentel: It doesn't take long… weeks.

Shivan Sarna: That's awesome. Okay.

Dr. Allison Siebecker: Actually, can I just point out that that is so incredibly important, what you just said, because so many people are thinking that if they take an antibiotic—in this case, rifaximin—it will mess up and destroy their whole microbiome. This does happen with other antibiotics. It's so important, what you just said.

Dr. Mark Pimentel: Yeah, we were surprised to see it as nicely as we saw it as well. There's always this concern of taking antibiotics. We've been giving rifaximin for 10 years, and we haven't seen any critical problems, no resistant organisms… none of that. So, I think we're on safe ground with rifaximin here 10 years later.

Shivan Sarna: That's huge. We've obviously been talking about food poisoning. We have gotten a lot of questions. Especially if someone's new, I just want to clarify that there are other underlying causes for SIBO and IMO.

Dr. Mark Pimentel: Well, yes. So, when we talk about IBS first, 60% are due to SIBO; and then on the constipation side, it looks like about 50 to 60% too (if you look at that data I just showed you) are IMO. So, the rest of IBS is a smattering of other things. And some of those things we can't figure out too.

But on the SIBO side, yeah, SIBO can be caused by adhesions. Anything that causes the gut to slow down will cause SIBO. But we now have studies that have come out from other groups that show that, if you made adhesions in animals, guess what goes up—E. coli and Klebsiella, same story as a regular SIBO. So, we're seeing all of this sort of microbiome work pan out in other causes of SIBO as well.

But remember, if there's another cause of SIBO, sometimes treating the underlying cause will be helpful. So, if you have adhesions, fixing the adhesions will make you stay better. So it's important to know the cause. And that's why the vinculin and CdtB antibody helps you get there because at least you know food poisoning is in part the cause.

Shivan Sarna: And once you've had food poisoning, you're more susceptible to getting food poisoning.

Dr. Mark Pimentel: Right! And this is a study that Mark Riddle, I've mentioned his name earlier in the program, showed. He showed that if you have IBS and you go get deployed to certain areas—he was working with US military at the time—that you're almost three times more likely to get food poisoning again.

So, what I think is happening is that the food poisoning damages the nerves of your gut, so that if you get food poisoning again, even if you have a small amount of Campylobacter, it's enough, the cleaning waves aren't cleaning them out, and they have time to grow there and become an infection and pass on to other people.

So, I think the Campylobacter and these bugs are damaging you so that they can use you over and over again as a food poisoning conduit. And that's what I think that's why they're doing this to you.

But look, we're going to break that cycle. That's what we're doing. We're going to break that cycle.

Shivan Sarna: The other thing is, the elemental diet, how do you see that working for the three gases? We've talked a lot about the antibiotics. But we always think of the elemental diet as a difficult-to-do but effective alternative. Do you still feel that way?

Dr. Mark Pimentel: Well, I think the elemental diet, what it does, is it starves the resources for hydrogen production. So, it doesn't matter whether you have the Christensenellaceae or Ruminococcaceae, they need food to make hydrogen, or the E. coli and Klebsiella, they need food to make hydrogen. And then, the hydrogen funnels it either into the methane or the hydrogen sulfide.

But the point is, you get rid of the source food, you're going to get rid of the hydrogen production. And then that will help either.

But having said that, we do know that it's harder to treat methane with the elemental diet than it is with the regular sort of hydrogen sulfide IBS-D.

Shivan Sarna: And so, if you're trying to reduce the hydrogen as food for methane, would taking rifaximin by itself (like if you can't get neomycin or a Flagyl strips), would that help at all because you're reducing the hydrogen?

Dr. Mark Pimentel: So, we do see some reduction for some pure "methanogens" with just rifaximin, but it's uncommon. I would say it's less than 20% chance of getting rid of your methane with just rifaximin.

But adding the two together, you get up to about 80%—at least in the clinical trial, that's what we saw. So, I think combining them is the way to go.

Remember, methanogens are not bacteria. There are archaea. All of our antibiotics were designed for bacteria. It just so happens that they work a little bit in those organisms.

So, we don't understand what exactly we're doing that brings the methane down, whether we're killing the two hydrogen sources, or whether we're actually killing the methanogen. We're still studying all of that.

Shivan Sarna: And the other thing I want to just quickly ask because it's coming in hot from all these questions (which is also for people who are new): multiple rounds of antibiotics is so unusual because we're so used to a one-and-done, could you just touch on that? And then, Allison, I'll let you take over with questions.

Dr. Mark Pimentel: So, if you look at the rifaximin target 3 trial, the people with diarrhea, it was a one-and-done for about a third of patients who responded… which was really fantastic. But remember, there's a spectrum of IBS. I can tell you, my patients with anti-vinculin antibody, it's usually not one-and-done. It's not quite that way. And the higher that antibody, the more—

I have patients where the anti-vinculin is literally at the top of the scale. And they end up, in my practice, being on chronic rifaximin. The moment I stop it, the cleaning waves are so bad that, as soon as they stop the rifaximin—I don't want people to be on chronic rifaximin. That's not the goal. But I have to help patients until we can figure out a way to make this cure. And so, that's the kind of stuff we do.

Shivan Sarna: So, Allison, I know I said you could have a question. But hold on, let me just finish this.

Dr. Allison Siebecker: Take your time.

Shivan Sarna: Thank you. It just went out of my head. Okay, multiple rounds…

And let's just get this out there about the herbs. There are a lot of people who won't be able to get access to the scripts affordably. And they don't want to take on necessarily the elemental diet. What's been your experience with herbs?

I know Dr. Siebecker loves both and has great experiences with both. But I just love to get your take on that.

Dr. Mark Pimentel: Well, as you probably all know, there was a study by Johns Hopkins that showed that a cocktail of herbs was as good as rifaximin. So, it is possible to get a combination of herbs that can be effective for this. You just have to do it under the proper supervision of somebody who knows what they're doing so that you don't have trouble.

So, I think there's a role for herbs in this. And that was a randomized control trial. That wasn't just an anecdote. So, we have data to suggest some of these herbal preparations are effective.

Shivan Sarna: I remember the other one. For treating the hydrogen sulfide, when you do treat with the rifaximin and that bismuth—and I know a lot of people's gastroenterologists are not going to have heard of that yet. We need to type out this transcript and have people distribute this to everybody's gastros (which I just authorized us to do a transcript, so everyone can have that to share with their doctors because I'm not sure everybody's doctor will watch a video). But for the bismuth, I know you've said that you just have people do some Pepto-Bismol. Can you just address that? Like is it a swig? Is it the pills?

Dr. Mark Pimentel: Yeah. So again, this is not a randomized control trial. This is just what our experience is using Pepto-Bismol. We used bismuth about 50mg. We give it 3 times a day with rifaximin. It's not FDA-approved for this as you know. But similar to H. Pylori, we're talking about trying to expand what rifaximin can do by adding the bismuth to it. And we see some good results with hydrogen sulfide quite commonly with that cocktail.

Shivan Sarna: And then, the idea about biofilms and combining it with a treatment, whatever that treatment may be, are you guys and gals working on more discoveries about biofilms?

Dr. Mark Pimentel: You have to stay tuned. We're going to give you some more data later this year on trying to get to where E. coli and Klebsiella reside in a special way so we hope that it would be more effective. So, stay tuned.

Shivan Sarna: Okay. Dr. Siebecker, handing it over to you.

Dr. Allison Siebecker: Wonderful, Mark. Thank you so much.

In that study you did showing that two types of SIBO or IBS that can come out of food poisoning, I just wanted to ask you just a clarifying question from reading the abstract—and I think you just addressed it when you spoke—but you had three clusters. The first cluster was similar to controls in that study. But in the abstract, the language said, in fact, they had lower wet stool weight compared to controls. And so that made me think are they going towards constipation? Am I just misunderstanding that language?

Dr. Mark Pimentel: Yeah, I think you're referring to the animal study.

Dr. Allison Siebecker: Yeah, yes, the rat study.

Dr. Mark Pimentel: The rat study… the animals went in three different directions.

It's sort of like if you got food poisoning, some people don't get IBS, right? And some people do. And because we're rigging the system to have more IBS with more CdtB toxin and more Campylobacter, we're going to get a higher rate than what's seen, in humans.

But what we're seeing is that, yeah, some of the animals who got the CdtB ended up with their microbiome looking similar to healthy animals. But maybe they had a leaning towards IBS-C. We have to dissect that further. And we haven't disclosed that information yet. But at least what they're not getting is the diarrhea side.

Dr. Allison Siebecker: Okay, great. And also, I was wondering, the organisms, the bacteria that are making the hydrogen sulfide, is it specifically the Fusobacterium variant and Desulfovibrio piger? Or is it not so specific to that? Because that was in the oral presentation at DDW. I'm just wondering… can we say that? Are you saying that? Or are you keeping it more Desulfovibrio and Fusobacterium?

Dr. Mark Pimentel: Well, so now, what we're doing is we're doing what we did with methanogens. Remember I showed you this slide with all the list of methanogens and where they are in the whole gut? We're doing that with hydrogen sulfide. So, I actually don't even have that data yet because we haven't finished that analysis. There's lots of Desulfovibrios and lots of Fusobacteria. So, we have to figure out which ones are the characters, where they are, how they're distributed through the gut, and all of that.

So, we're working on that now, but I'll get you more details probably within the coming months.

Dr. Allison Siebecker: Oh, that's fabulous!

Dr. Mark Pimentel: But my guess is it's not going to be just the Desulfovibrio piger or the Fusobacterium varium. We just find that they are more potent to produce hydrogen sulfide. So, we were able to see that signal more strongly. Just like Methanobrevibacter smithii is the most potent methanogen for producing methane, but there are some weaker elements that do produce methane as well.

Dr. Allison Siebecker: Oh, that's fascinating. And that study was also so fascinating with the methanogens characterizing them throughout the whole small large intestine. And there was a conclusion in that that was so interesting. You said 50% of the study participants actually didn't have methanogens in their large intestine.

Dr. Mark Pimentel: Yeah. So, there was this back-and-forth argument—not just us, but in the medical community—as to while methanogens…

You know, Michael Levitt, just going back to Michael Levitt who did the hydrogen sulfide gets better with the with bismuth. During all the years he was doing the work up until the 1990s, he said, "Methane doesn't do anything. Methane is inert." And he said, "And the methanogens are only in the colon." But he didn't have access to the small bowel like we do so.

So now, there's this push-and-pull: are methanogens only in the colon, are the only in the small bowel, are they in both? And I think what we're finding is, when it's a problem, it's in both. But more commonly, it's small bowel.

I still think we're going to leave it as IMO because we can't know in any one individual whether it's both or one or the other. So, I think it's wise to say that it's both, but more of the small bowel—just how you stated it.

Shivan Sarna: Can I chime in, Allison?

Dr. Allison Siebecker: Please!

Shivan Sarna: Stool testing… for a lot of people asking, "Well, I have high fusobacterium spp. In a GI-Map"—that's just an example. But could stool testing indicate anything for IMO if you already had the test?

Dr. Mark Pimentel: Absolutely yes. Do a study where you show fusobacterium at this level correlates with hydrogen sulfide at this level correlates with diarrhea at this level… I would be very satisfied with that. The problem is… that's not being done.

So, you can't just say "fusobacterium bacterium is a little up, and therefore it's out of whack, and you knock it over the head" because it's not that simple. And to be honest, when fuso's up, it's not up like this. It's catastrophically up.

And the same with methanogens… when they're up, they're not just up, they're up. It can't be simply like a bar thermometer of where things are. It has to be like something very significantly elevated.

At least in our sample sets, that's what we're seeing. So, we could actually, in our data, prove what the levels are that correlate. And we may proceed to do that. But I think just do the research, and then we'll be more believing what the stool studies are saying. But it's always more complicated.

Shivan Sarna: And I just want to address the whole audience right now about that. This is tremendous. This is incredible. Obviously, you have just been listening to it, and your minds are probably blown like ours are. But it comes back to also a combination of hope in patients because it takes a long time. You've been working on it for how long now, Dr. Pimentel? Like seriously, when did you get started in all of this?

Dr. Mark Pimentel: Twenty-six years? Yes, 26 years, 27 years?

Shivan Sarna: And there's some people on this call that weren't born yet.

So, really, for those of you who are frustrated and may be sad, but then there's another group of you who are like, "Yeah, we're getting closer," I would invite everyone to join the group that's psyched that we're getting closer. This is hope. This is incredible.

How many conditions can you think of out there that are not getting paid attention to and that science hasn't been able to crack the code at all for ages (and yet, thank goodness, other progress is being made as well).

So, this is just exciting. And it feels very, very slow in some ways. Dr. Pimentel will feel the slowest, I'm sure. But for those of you who are frustrated, hang in there. This is hope. This is real. It's very exciting actually to be witnessed to all of this, Dr. Pimentel from the lab, I mean, who else gets this kind of access? Fortunately, with the Internet and good souls and all of the progress and funding, we've been able to connect and get the word out even more… which is so cool.

But please… don't give up hope. Listen to what he said. We're going to get the transcript out. It will take not instant because I have a real human being who does it who's smart. So, give us a week for the transcript. And we will send out the replay ASAP. I would say that one can go out within 24 hours. And then, that link will also take you to the transcript.

But also, the link that we're going to send you takes you to all of the presentations that Dr. Pimentel has done for us over time… which is years and years. So if you're really super "Wow! This is amazing!", like Dr. Siebecker was saying, "I read this study, and this study, and it's been growing and growing and growing," watch some of those (you can even watch backwards if you wanted to). But this is the most and latest and greatest and cutting edge. So, if you only have an hour, this is the one. But it's very exciting.

So, I want to give everyone a reminder of hope.

Dr. Pimentel, give us some more hope, please.

Dr. Mark Pimentel: You know, I saw a comment come across there. Some of us are older, and time is not… you know? I know. I mean, I understand. I can only go as fast as the money comes in to be able to do this, and the people and the resources and

all that. The work that you see here is through blood, sweat, and tears, finding resources here, there, and everywhere. The NIH isn't funding this. I wish they would. I wish we would get funding like that, and we could grow our team and double our team, and quadruple our speed. But this is what we have. We're doing our best.

And the funny thing is we've got this new Rome criteria coming on. I'm not trying to bash Rome. But this new Rome criteria coming out, and there's so many people on the Rome criteria trying to redefine IBS one more time. Where's the studies on the cause of IBS? Let's go! Let's get some other people. I mean, I'm doing it. There's a couple of others in the US that are trying to find the cause. We need 20 or 30 centers in the US trying to find the cause alongside us. And they're just not there because the money's not there.

So anyway, that's not a pitch. That's more of just saying, "Look, I can only do what we can do as fast as we can do it with the resources we have." I wish we could help patients faster.

Shivan Sarna: I know you're not doing the pitch, so I will... how can we donate? Where do we go?

Dr. Mark Pimentel: Sorry, I didn't mean to set that up. But my Twitter account has the link to it, the donation page. You can donate there if you want. But if it's something larger, then we have a system at Cedars that can allow that to happen.

Shivan Sarna: And that's just me being overly enthusiastic. It makes him uncomfortable because he's a scientist. But I am a band leader (which is fine with me. Everyone has a role to play).

The other thing that I wanted to recommend to everybody is to get his book because the book is phenomenal, phenomenal, and very easy. It's a quick read, but super dense with information.

Somebody was asking, "How can we relay this information to your gastroenterologist or your doctor or your nurse practitioner, and do it in a way that they wouldn't be feeling disrespected?" We all have our egos and stuff. I say giving the book is a great idea. But also, get them the transcripts. Any other suggestions, Dr. Siebecker and Dr. Pimentel on that?

Dr. Mark Pimentel: No, I think educating your physician is important And hopefully, there's some physicians online as well. We do that all the time. I'm speaking at various conferences. And that helps encourage the information to be disseminated.

And look, 80% to 90% of gastroenterologists in the country are doing rifaximin which is a big change from what it was 10 years ago when nobody understood the microbiome at all. So, we've come a long way. And we're going to continue to push, and continue to push, and continue to push, until at the finish line of some of these roads.

Shivan Sarna: And here's a shameless plug that it's on sale right now at 15% off, Healing SIBO, my book that Dr. Siebecker wrote the foreword for and read every word of. It is a great companion. It's also my story, but there's also recipes and stuff. So lot of good practical information there.

Dr. Pimentel, when it comes to the next sort of conference that you're doing where you're going to release another batch of awesome information, are we looking at six months, a year? What are you doing at 3 o'clock on that day?

Dr. Mark Pimentel: You always want to get that first cut. This is the first cut of this data which is fantastic. So yeah, I mean probably by AGC which is in late October, we'll have a lot more information and some more studies that have come out. We're publishing a flurry of papers, some were not part of DDW (so you'll see the more detailed information). So yeah, probably late October, early November would be another good time.

Shivan Sarna: Okay. Dr. Siebecker, did you have any other questions before I grab a couple?

Dr. Allison Siebecker: Yeah, I did! Mark, you were co-author on a study that came out that you just put out that I thought was, again, so important for patients struggling with their doctors who won't order them the breath test for SIBO when they have IBS? Can you talk about that study you just put out?

Dr. Mark Pimentel: Well, I think the challenge we have is that—and it's probably more the case in areas that are not near academic medical centers, people call it "rural areas." But I don't call them rural. I call them just areas of the country where it's more

the country physician, not necessarily somebody at a university hospital. If I was out there, seeing 60 patients a day, I couldn't keep up with the all the new things as cutting edge is what we're talking about today. I just can't! They're studying cardiology, liver, lungs, and all these different things all at once. I have to learn everything.

So, it helps to keep them up-to-date. And sometimes patients can help in that process. And I think we're all trying to get out there and reach them in various ways. But they don't necessarily know.

And there are doctors who are still stuck in the idea of antidepressants. This is 1990s stuff. Antidepressants are the first line of therapy for irritable bowel syndrome. And based on evidence, randomized control trials, there's no randomized control trial of a tricyclic antidepressant using FDA endpoints. So this, it makes no sense. And hopefully, patients can educate their doctors, too.

Dr. Allison Siebecker: Yeah, I just thought it was so important because you've had more than one of these studies come out where the conclusion is, in IBS patients, there's incredible evidence here to run breath tests to check for SIBO. This was just a DDW abstract. I'm hoping it will come out as a full paper. And then, patients can take it to their doctors.

Dr. Mark Pimentel: Somebody just mentioned from Germany (I just saw the screen thing come across) that there's a complicated story about Europe and SIBO. And it has a lot to do with rifaximin not being approved for IBS. It's interesting because Canada—if there's anybody from Canada, shout out, because I'm Canadian. In Canada, rifaximin wasn't FDA approved (or their FDA equivalent) up until about a year and a half ago. All of a sudden, FDA has approved. It's approved in Canada. And all the doctors want to know about it.

Well, we've known about it for 10 years! Why do you now want to know about it? Well, because they're actually seeing it in their patients, they're getting better. And they're now starting to say you, "Yes, IBS is microbiome disease."

And so, all of a sudden, Canada has a great interest in this. It's not approved in Europe for IBS. The doctors find it expensive, they don't give it, they can't give it. They can't get that experience. "Europe is tough," somebody just said.

Shivan Sarna: I just wanted to ask you about addressing prokinetics. We talked a lot about it up until then. So for anybody who's new, and has just started learning through this particular session, could you just educate us briefly on what a prokinetic is and why it's so important.

Dr. Mark Pimentel: I didn't get into that part of it because, remember, the migrating motor complex, the wires being disconnected because of the antibody, the anti-vinculin which is so important. But the way I describe this to my patients is that, when you have the anti-vinculin antibodies, and the wires are not getting to the right circuit, what I tell people is, "Imagine you go into your house, and only half the lights, the wires reach the switch. That's what happens with SIBO." You turn all the lights on that can turn on, and it's still dim in the house. You can't make the wires connect because that would be getting rid of the anti-vinculin antibody (which we haven't quite mastered yet). But you can turn the volume of the lights that do work up. And that's what a prokinetic does.

So, the lights that are on are brighter. And that helps make up for the lights that are off. And that's what the prokinetic does. It helps keep you from needing the antibiotic again for a more longer period of time.

And we've shown that in trials. I didn't have time to show you that data. But that's published by us and others as well. And so, yeah, those prokinetics do work. And prucalopride is the one we tend to use; although I know some people will use low dose naltrexone. We've also used low dose erythromycin. That's something we do often as well—but after treatment. We use that after treatment.

Shivan Sarna: And how long can someone stay on that in case their antibodies are still ruling the roost?

Dr. Mark Pimentel: Well, the goal is to make you as normal. as possible. So, we use that. Let's say, for example, if the anti-vinculin is very high, we might use the

prucalopride at bedtime. And then, over 3 or 6 months, we might decide to wean a patient off of it.

If they're doing terrific, if that's the case, then we can get them off of it. But if, as soon as we start weaning, the symptoms start to relapse, then we put it back up again.

So, it just depends on what the patient is telling us and how they're feeling.

Shivan Sarna: I just wanted to address that because a lot of people are afraid of doing multiple rounds of antibiotics for example. So, thank you for addressing that—and the same thing with the prokinetic.

And have you found ginger at all to be helpful?

Shivan Sarna: Oh, ginger is a great anti-nauseant. It's not, in my view, a great antibiotic. I mean it's not a good prokinetic that I'm aware of. And I've never studied it in migrating motor complexes. So I don't know if it does anything there. So it has benefits, but it doesn't hurt for sure.

Shivan Sarna: So, we have someone from Poland. I'm so excited. My book just got published in polish. So go find that. Hello, Poland!

And then, fiber, there's a lot of questions about fiber. I know when I first went to the gastro, the infamous doctor-run-three-miles—he told me to run three miles, and that was a great laxative. I was like, "I can barely move here, buddy!" But anyway, he also said here's some Metamucil. And that was very upsetting and disasters for the feelings of my intestines. Help us understand the role that fiber could or couldn't (should or shouldn't) play in a SIBO/IMO patient?

Dr. Mark Pimentel: So, fiber is a fuel for making hydrogen. So, more fiber means more hydrogen, means more methane or hydrogen sulfide. That's the downstream consequence… so not good.

So, anything that's not absorbed but is a carbohydrate base is a problem. And sucralose is the worst! Literally, I just talked to a patient this morning who didn't know that the gummies he was taking as a vitamin had sucralose in it. He was complaining his SIBO might be back, and this and that, and it was the gummies that had sucralose that were giving him so much problem.

So, we have a lot of sucralose and these non-absorbed carbohydrate fibers. It has been put in Cheerios. Fiber has been put in everything. It's causing a lot of bloating.

Shivan Sarna: These are the most common questions that come up over and over and over again. And the other thing is, you know, Dr. Siebecker, just on a side note, has created the SIBO Pro Course. So tell your practitioners about it. if they're really interested in helping you and learning about Dr. Pimentel's research and protocols that have worked for her, the SIBO Pro Course is a great idea.

And then, for patients, we have the SIBO Recovery Roadmap® that goes through everything that Dr. Pimentel has been talking about for protocols that Dr. Siebecker has also used.

And what about pelvic floor therapy, pelvic floor issues? Have you seen that play into this into this, into SIBO and IMO particularly?

Dr. Mark Pimentel: Pelvic floor issues are relatively common and can factor into—well, pelvic floor issues factor into diarrhea IBS. For example, if the pelvic floor is too relaxed, when you're having your diarrhea IBS, you could have incontinence. You can have other problems (which can create a lot of issues. It's very difficult to have incontinence. That's a tragedy).

On the constipation side, there are pelvic floors that are too tight, so to speak, or don't relax enough. And often, the IMO is negative. So, if you have a negative test through the breath test for IMO, look for pelvic floor dysfunction. That's the first thing. And Dr. Rao will tell you that on his conversation with you, that pelvic floor dysfunction is critical to look for—especially if, after the breath test, there's no methane

But even in the methane patients, if they get marginally better, or they get better and the methane is gone, and they still have some residual problems, you've got to check for these things.

Our goal, you know I say this in analogy… if you have IBS with diarrhea, you know what would make you better? Morphine! Morphine makes a pain go away. Morphine makes the diarrhea stop because it's constipating. And you won't remember the bloating.

But no! You can't give morphine. The point is it's covering up symptoms. Covering up symptoms is not a treatment for the disease. Finding out what the cause of the disease, and treating that, makes the patient normal.

I want to make my patients as normal as possible, so they can go out with their friends, go to a movie, get on an airplane, and not have to worry about diarrhea. That's the goal.

So, I'm just saying you can always cover up symptoms with drugs, but it doesn't mean you're making the patient better. It's just giving side effects.

Shivan Sarna: Absorb that beauty, that chunk of gold, as we like to say. That's gold.

The other question that I had was—well, actually, announcement. Dr. Siebecker and I are constantly doing free webinars, Q&A's, and that kind of thing. So, be sure to be reading your emails with those invitations. Join our Facebook group that we have over 24,000 people in talking about these topics, the SIBO SOS® Community. I know there are a lot of you watching this right now streaming there, so thank you.

Let's start throwing some love into the chat for Dr. Pimentel. Thank you so much, sir, for being here, and for sharing your wisdom with us, and giving us the scoop. You know we love that!

Dr. Mark Pimentel: Thank you so much. It's so good to have talked to you both today and everybody online. I'll just keep doing what I'm doing and keep updating you as much as possible. And I'm sorry if I can't help everybody. But certainly, we'll do our best and continue to progress this.

Shivan Sarna: Oh, we really appreciate it. We really appreciate it.

Dr. Allison Siebecker: I mean, we are so fortunate to be living in a time when this research is occurring. I mean, I couldn't even believe it when I first found you were doing this work. And I thought, "Well, thank God somebody's doing something to figure it out."

We can't figure out how to treat it, cure it, make it go away unless we know what it is. So, that's what Dr. Pimentel has been doing. Thank you so much!

Dr. Mark Pimentel: Thank you.

Shivan Sarna: Take care, Dr. Pimentel.

Dr. Mark Pimentel: Alright, bye bye.

Shivan Sarna: Thank you. Bye bye.

If anyone else wants to just stay on for a minute, we'll let you know that—thank you, Dr. Siebecker, as always.

Dr. Siebecker and I do a lot of these free webinars throughout the year. We do have those courses if you're Intrigued and interested. And they are aligned with everything Dr. Pimentel is doing. So, that's super, super important that you realize there is support for you…

Dr. Allison Siebecker: …particularly the treatment information. I saw so many questions coming in on treatment that we discuss over and over again in free webinars that we give. So, if you have not come to attend some of those, please do that. We can answer your questions.

Shivan Sarna: That is our mission, is to help you get educated so that you can be well. Dr. Siebecker is a SIBO patient. She and I both had it—we didn't know each other when we were five, but we both got our SIBO when we were 5. And so, I'm so glad that she and I are friends and colleagues.

And please do go to our Youtube channel as well, the SIBO SOS® YouTube Channel. Dr. Siebecker, her website is SIBOinfo.com.

Dr. Allison Siebecker: Tons of information for your questions, folks, on these resources—SIBOinfo.com and SIBOSOS.com.

Shivan Sarna: Those are two fabulous resources for you. We love you. We appreciate you. We're thinking of you pretty much 24/7. And we will be sending out the recording ASAP. Give us 24 hours (but I plan on doing it much sooner than that). The transcript, give us a week.

And remember, when you get these links (and even I think when you registered it for this through Zoom), the registration page had all of Dr. Pimentel's other talks that he's

done for us. So, I know you had plenty to watch between the time you registered and today. But that page is a rich, rich resource. And we'll include it with the recording that we send out today.

Anything else, Dr. Siebecker?

Dr. Allison Siebecker: No, I think what he has put out in this recent series at DDW is just incredible! There were other studies we didn't get to talk about. They're actually really phenomenal. For those of you who get my newsletter, my quarterly newsletter, you can sign up at SIBOinfo.com to get that. I went over all those studies. I put them all in there. There's some really amazing things that I just wish we had even more time with him to discuss. He's just really put out so much information in this last batch. We're really getting the full picture coming together.

Shivan Sarna: Yeah, it's exciting. And the fact that, you guys, he just gave us an hour and 50 min—the three of us got on at 9 Pacific, 12 Eastern—that is so, so generous of him. And I know he's not here listening right now, but I'm just putting it out to the ether. Thank you, thank you.

And gratitude to all of you, and kudos to all of you, for taking the time to show up or watch the replay. I know you have a lot of other things to do. But I also know that you are honoring yourself and acknowledging that you deserve to be well by taking these right steps and action in educating yourself.

And please spread the word. What you learned today, please teach other people because that is how this is going to change. And definitely talk to your health providers about all this information.

Share the link when you get it, et cetera. Go to the Youtube channel. We have 20,000 hours, Dr. Siebecker, now of hours watched on our Youtube channel, SIBO SOS®—which I'm not even paying attention to it, I hate to say it. We do something, and we just put it on there. So I'm just so pleased, but it also shows the need. So please do.

Thank you very much. I recognize so many of your names from coming so many times. And if you signed up for this through the Zoom link, then we have your email

address. I think that that will mean that you'll get at least the recording. But you can also reply and say, "Hey, make sure I'm on the email list."

Dr. Allison Siebecker: And people were just asking how do they sign up for my newsletter? My free educational website is SIBOinfo.com. That is where you sign up for my newsletter where I always give a quarterly of all the studies that have come out.

Shivan Sarna: That's such a cool site, SIBOinfo.com. And then, SIBOSOS.com, that's a great place to get like the testing ebook. And there's my IBS vs SIBO ebook. But I also have the schedule of the events that we're up to.

The main thing is open your emails from us because that's where the goodies are.

Also, 15% off at Fullscript which is a huge dispensary for professional grade supplements that Dr. Siebecker has allowed us to have access to. That's a really, really big deal. And I know a lot of you take advantage of it. Normally, you got to go to the doctor's office. So, we really appreciate that.

We also have a new friend in Rupa Health. They are giving us the ability to share with you functional stool tests and a few other really cool tests. That's going to be I know a tool for a lot of you. It's a clearing house for tests. Allison picked some that she really likes. Did you want to just talk about that for a second?

Dr. Allison Siebecker: It allows you to get functional stool testing and some other tests directly. You can order them directly. They have a staff physician that will give you a complementary order or prescription through that dispensary. And we'll be adding more tests there.

And Shivan, I do have to go. Thank you.

Shivan Sarna: Good bye!

Dr. Allison Siebecker: Thank you everyone. Goodbye!

Shivan Sarna: Bye bye.

We do email a fair amount. So just pick and choose what you want. And also, there is a 7% fee to Rupa for those functional tests. You know, for Dr. Siebecker and I, it was an

easy yes for us. Here's why. And do share the information you receive with your practitioners. But a lot of people have to go to a practitioner before they could even have access to some of those tests. Some of you are very savvy patients and really want to compare your last stool test with a newer one, but don't want to pay for a doctor's visit necessarily (I'm not telling you not to go to the doctor. I'm saying do!) However, sometimes getting one of those tests in between visits or whatever can be really handy. So Rupa does charge a 7% service fee. I think it's maybe an $18 charge to get with the doctor to sign the thing.

But look, go to Rupa Health, it's right there. Check it out! If it's a fit, great. If f it's not, that's fine. But we wanted to share that with. We're really, really glad that that service exists.

What's also cool is you can keep all of your functional tests in this one portal. If you're like me, I can't find tests from five years ago and stuff. I would love to have a place—I know I saved it on my hard drive. I know, I know. But it's very cool to have them all in one place.

Okay, Rupa Health is amazing. I know a lot of practitioners use them. And they reached out to us, they're like, "Hey! We need to get the word out." And they have access to thousands of tests, but Dr. Siebecker cherry picks them.

We will add the good links to the replay area. If you use our links, you don't need a code for Rupa or Fullscript. You just have to use the links we've been providing (and that we will put in the replay). Don't worry about copying the links. Click the email that then takes you to the replay for Dr. Pimentel. You can find them there. And you'll also see all of his other talks.

And don't worry about it! The tech worked for most everyone. There were two people that did not have good tech. Don't worry! I'm sure the replay is going to be amazing.

So, Shivan Sarna here saying thank you so much for being with us. Please do join the Facebook group, the SIBO SOS® Community, so we can stay in touch.Join us for the free webinars we're talking about in the emails. We could do great masterclasses all the time. We just finished one on—oh, we just finished one on constipation and stool testing and GERD with Dr. Steven Sandberg-Lewis, Ilana Gurevich and Stephanie

Kimball. That was an amazing one! They're just some really fun stuff that we're up to these days.

Anyway, with that, I'm going to stop the recording. Thanks for being here.