Digestive Disease Week 2023 Research Update (May 2023)

with Dr. Mark Pimentel

Your host Shivan Sarna and Dr. Allison Siebecker

How to search this transcript

Looking for a specific topic or clip from this session? Press **Command + F (Mac)** or **Control +F (PC)** to pull up the search bar, then type in the key word or phrase you're looking for. Press "enter" and the PDF will scroll down to the section in the transcript where your keyword/phrase appears.

Shivan Sarna: Hello and welcome. I am your co-host today, Shivan Sarna. I am the founder of SIBO SOS® and the author of the book *Healing SIBO*. That's the Polish version right there of the Healing SIBO book, I'm very proud. And I also have my co-host, Dr. Allison Siebecker, one of the leading advocates for connecting medical doctors with naturopaths with patients on SIBO and IMO. Her site is SIBO info.com.

We've co created courses together for the patient population SIBO recovery roadmap, and she has created a beautiful professional course called the SIBO pro course. And our star today is Dr. Mark Pimentel who's going to be bringing us in on this annual tradition, an update from digestive disease week, also known as DD W.

This is 2023 where he has the foundation of his work as well as the newest research and when I say the foundation of his work, no pressure Dr Pimentel, but if anyone's going to find a cause for SIBO, IMO and IBS, we know it's you. We need a cure.

Dr. Siebecker: That's what he's working on.

Shivan Sarna: That's right. He's coming in hot from Cedar Sinai, and the medically Associated Science and Technology program right now, where he works with a brilliant team, helping to solve the problems and rebalancing ultimately the microbiome because of this work that he's devoted his life to, he's the one who has

developed the first blood tests for irritable bowel syndrome. For its connection to food poisoning. He's the one who made the team and discovery of Rifaximin, as a treatment for IBS, SIBO IMO, and describing the relationship between IBS and Small Intestinal Bacterial Overgrowth, and Intestinal Methanogen Overgrowth, determining the relationship of IBS and SIBO as an autoimmune condition. Also, of course, the one who has created the three gas breath test from Gemelli labs, the Trio-smart test. Those are just a few of the things he's been up to.

Dr. Siebecker: You left out at least 15 monumental discoveries. Thank you, Dr. Pimentel.

Shivan Sarna: Thank you so much for being here. And for all your good work. I'm going to hand things over to you sir.

Dr. Pimentel: I'm excited. Let's get going. This is our office, it's not a full backdrop, this is a real deal. Thank you for inviting me to present the updates from DDW (Digestive Disease Week) in context of the work that we've been doing here. For those of you who've seen this presentation, you're gonna say, Oh, he's talking about the same things again, I am actually not, as you'll see, we have at least 20 new slides in this because so much has happened. The foundations of the work - are the foundations of the work.

I want you to understand that if you listen to the last year or previously and then you listen now you will see how what's been built on the foundation because you now understand what the foundation looks like. And then the new things and how they plug into this puzzle, as the puzzles coming together more and more. So if it's boring, because you've seen it before, believe me it won't be boring later. So we'll get to it.

As I mentioned this is what we do, we're trying to develop the things that patients need. And to a great extent what we try to incorporate in everything we do. And I don't talk about it in my slides, but I think it's worth noting everything we do tries to also reduce health care costs in the spaces we're working in. And we've done the cost analysis for the breath testing for the blood testing, for the drugs that we are trying to develop to show that if you find IBS and SIBO early and treat it sooner rather than going through shenanigans of testing, you're going to save money and save healthcare costs. And I've seen too many times, patients come to me after a 5, 6 or 10

year journey of $20,000, and co-pays when they might have been able to make an assessment and understand their illness sooner, whatever that illness is.

And so I think all of this is really important to understand. I want to take you back, this is a new slide, circa 1996. This is about when I started fellowship here at Cedars Sinai, this is what we thought of IVs, or what the field thought of IVs there were no FDA approved drugs at that time. Maybe it's early life trauma, maybe it's anxiety, maybe it's depression. IBS was a disease of women. That was what they people thought, this is a literal quote from a physician, "IBS is a disease of hysterical women". Literally a quote. Shocking, right. And IBS was a diagnosis of exclusion, so you applied the Rome criteria, but you had to have nothing else. It's a diagnosis of exclusion. A wastebasket diagnosis. And then these are the things that people were trying, there were studies that show some benefit to psychological therapies, antidepressants, antispasmodics, laxatives for constipated patients. And that was it, so if your IBS causes constipation, you take a laxative. If you're having diarrhea, you take an anti diarrheal or maybe a tricyclic antidepressant. And that was the story. And that has been a story for some people, even to today, those who don't listen to the new developments because there are a lot of new developments. I pause on this a little bit because some of the guidelines for IBS, even today, the guidelines say well use an anti diarrheal, for IBS. And why because it's safe, and it's inexpensive. And the answer to that is yes, it's safe, and it's inexpensive. And I just finished saying inexpensive is good, but an anti diarrheal taken chronically. Can you imagine a guideline for Crohn's disease, where the first line therapy is an anti diarrheal drug, it will be hearsay and in the Chrone's space because yes, and anti diarrheal would make the Crohn's diarrhea better, but it's not treating the illness. And yet here we are still in 2023.

While we recommend an antidiarrheal first because it's cheap and it stops the diarrhea. Rather than focusing on treating the cause. I like starting with this point because I think you have to understand how physicians still think the guidance by the society is still in some ways promoting not a treatment for causes of IBS, but rather symptom improvement only, which is shocking.

As you've seen this slide before, maybe you haven't, but this is what we're going to cover, but we're going to cover it in a much greater detail because we have so much

more information. You can see here that it all starts with food poisoning on the diarrhea side of IBS. So you get sick, you went on a vacation to some country, then you eat some bad food, you get diarrhea, and then ever since then your bowels have never been or never returned to normal. When we've identified the toxin that we think is causing this cascade, we've identified that that creates auto immunity to a protein, vinculin and that changes the nerve function of the gut. The small bowel nerve function is diminished, you get a reduction in the special cleaning waves of the gut. And if you don't clean your gut, it's like eating off your plate without ever putting it in the dishwasher over and over. You get a buildup of bacteria on that plate or in this case the small bowel and you get bacterial overgrowth and I'll show you all the evidence for that and be particularly excited about the new depth in which we now understand SIBO and then of course you treat with an antibiotic. Rifaximin is the only antibiotic that is FDA approved, but it is FDA approved for IBS so that's pretty exciting.

Let's start here on the left which is E. coli C. jejuni Shigella Salmonella, they can all cause IBS. But what's the evidence? Like the primary evidence that food poisoning leads to IBS. Really one study, it breaks down to this one study by the Mayo Clinic. And if you look at the top the top are bacterial causes. And one in nine people who experience food poisoning will develop irritable bowel syndrome.

In 2017, this paper, it's very clear food poisoning precipitates irritable bowel syndrome will stop. Okay, so now we have to figure out how that works. Why that happens.

What I want to explain to you before we get into this, is that this happens to explain, probably, about 60% of IBS. Remember in the beginning I said IBS is a diagnosis of exclusion, historically. You do a scope, you don't find anything, you do some blood tests, you don't find anything. Okay, it's IBS. If you take leftovers, and you put them in, in a bin, that some of them could be a SIBO. But we're going to talk about some of those patients could be celiac patients, or EDS patients or various other diseases. We never believe that SIBO and post-infectious IBS is the cause of all of IBS because IBS is just whatever is left, but to account for 60%, that's a big, big thing.

Here we go. Can acute gastroenteritis post SIBO or IBS? And the answer is yes. So putting this together, we did an animal study. And this was all the way back in 2008. We were already thinking about this. I have a lot of fun stories about the CdtB toxin

which I don't want to waste your time on but really cute and fun, interesting stories about how we thought about CdtB toxins and got to that but Campylobacter on the right is given to rats on the left placebo to rats. Of course the rats got sick.

They completely recovered after about a month and then we waited three more months, so the total study is four months. And then we were able to see that the rats who receive Campylobacter now 27% of them have Small Intestinal Bacterial Overgrowth, whether it's due to DNA or jejunum ileum. That's the first part of the small bowel, the second part is small bowel third part is the small bowel.

That's what Duodenum and Jejunum mean, that 27% have overgrowth now, not only is that true, but if you focus on the purple column on the far right, you can see that if you got Campylobacter, which is C+ that's the food poisoning, and that Campylobacter causes the rat to have SIBO, which is the SIBO plus, those rats, 84 85% of them had altered bowel pattern.

And they also had increased rectal lymphocytes, which is what we see in humans with post infectious irritable bowel syndrome. So we had an animal model for the first time where it mimicked what we see in humans with an organism or a bacteria Campylobacter, which is a form of food poisoning, that is the most common form of food poisoning in the United States. So now we have a working model where we can start to dissect and figure out okay, what's going on here.

But what's going on here now 2008 - 2022 14 years later. I'm not going to go over all the studies because it's way too much for this presentation, I will just go over this slide, which sums it all up.

[13:41]

This is called the Bradford Hill criteria. The Bradford Hill criteria is a very strict set of guidelines on cause and effect when it comes to diseases caused by bacteria. So the question posed to the Bradford Hill criteria is there enough evidence to say Campylobacter causes IBS as one of the pathogens and it meets all the criteria which is not easy to do?

So this was published in 2020 18, and pathogens and disease and clearly Campylobacter causes irritable bowel syndrome. But how does that work? And this is where the toxin CdtB comes into play, and how it's affecting you and making you produce an antibody to yourself.

Well, I've already mentioned that all four of these organisms, Shigella salmonella, Campylobacter, E. coli, they're all bad organisms, you travel somewhere or you eat at a bad restaurant and you get food poisoning. These are the kind of bugs that cause disease, acute disease, so you get diarrhea. And then a few days later, it goes away.

The bacteria of any of these four, they're gone after a week, let's say or even a month. You can't find them in your gut anymore, but they did their damage. and part of their damage is with this toxin that they all share. And it's called Seidel, lethal distending, toxin B, or C, D TV. What CdtB does is it makes you form an antibody to that toxin. But part of that toxin looks like a protein called vinculin, which is in the nerves of your gut. And you can see the vinculin.

These are cells and we just use my mouse here, the green are the scaffolding of the cell to keep the cells shaped. It's called actin. And at the end of actin is vinculin, which is like a little motor that moves the cell to you can see the cells kind of reaching out to grab onto the next one to attach. So the vinculin doesn't work well, the wires can't connect to each other.

And I think that's the best way to describe what happens if you mess with vinculin. And you have this antibody, which I'll show you in a minute. So what's happening is that these cells, I know I showed you sort of cells this way, but now we're looking at them in a little bit of a different way.

These are the cells, the brown ones that are called interstitial cells of the hall, you don't need to remember that you just need to know that these cells are what make the cleaning waves of the gut go. And they need to be connected. So they need to be close to each other. And then their little, side, tentacles connect to each other like wires along a chain.

And so these wires along the chain need to be connected. If the rats got Campylobacter, but did not get SIBO, the chain is there, but it's a little bit less

impressive. In the rats that got SIBO the chain is broken, you can see one cell here, but you really can't maybe there's one there, it's hard to know, but the cells are diminished. And you can see that the number of cells when you count them blindly. So we didn't know which group was which. And you count them, the number of cells is lower in the group that got Campylobacter and that was treated with SIBO. So this is what's happening. This is how it happens.

So you have this nerve damage, and then you get bacterial overgrowth. Well, we actually showed this all the way back in 2022. I know the stream of thought is to go from left to right in science. But sometimes you get scattershot. And you have to start to put together the pieces is sort of like actually literally doing a puzzle where you're doing the face and the head because that's easier than the trees in the background, which is harder when you're putting pieces of a puzzle together.

But we already knew back in 22,002, that if you have IBS and SIBO, the number of your cleaning leaves of the gut, which those little cells I showed you on the last slide are controlling are down a lot down not only that 50% Half of IBS patients who SIBO we didn't detect any cleaning waves at all. So a bunch of zeros down here that are averaged into this, this final average. So the cleaning waves aren't working. And this is a known cause of SIBO all the way back in 1977, no cleaning waves, pore cleaning waves, you get bacterial overgrowth.

And that's sort of how it happens. So let's get down to a little bit more nitty gritty on the CdtB toxin. And I know this is going to get into some really dense science, but you need to know how important CdtB is and is the root because when the root of a disease, then you can root it out and cure it. And so this is a very big focus of our research, especially in the coming near future years. So we said okay, so if CdtB so it's not Campylobacter.

It's not Shigella it's not salmonella. It's the CdtB toxin that does all of this. If we just give the rats CdtB that's it, nothing else. And we use it like a vaccine like you to get the COVID vaccine in effect is almost identical. You take one dose three weeks later, you take the second booster. That's how we gave COVID vaccine. We do the same on the rats with the CdtB toxin.

Well sure enough, they didn't have antibodies to CdtB four there were clean rats, they didn't see Campylobacter. After the CdtB immunization of course the antibodies go way up. But look what happens to vinculin antibodies vinculin We're not giving them vinculin We're just giving them CdtB vinculin antibodies went up. So they were able to develop autoimmunity as a result of being exposed to CdtB. And only CdtB. That's all the rat song. We didn't put it in the gut. We put it in their arm under their skin as a vaccine.

They got SIBO so CdtB and Tea parties create SIBO. And that is a really important finding not only that they had reduced vinculin expression in their gut. So we were able to see that the CdtB antibodies are damaging the vinculin going on in the gut. So it kind of works like this, you get food poisoning, this toxin goes into your body and you're reacting to it.

So you form antibodies to this part to this part to this part, because all of its foreign, you want to get rid of this toxin. But one of the antibodies is similar to the protein sequence in vinculin. And that's called mimicry. The CdtB is tricking you to form antibodies to yourself, and then you get a lot of these bad changes. Well, this was DW last year now this, this paper is in process of being published. So it'll be finally published, A few weeks, we hope. And so but it is public information because it was presented at GW.

But it's very important to repeat that experiment with CdtB. And again, no antibodies before that toxin, a whole bunch of antibodies after the toxin, the wet weight of the stool went up because of the toxin and the antibodies, and the higher the antibody was, the higher the stool wet weight was. So the antibodies are driving the phenotype or the presentation of diarrhea in these animals in this second more detailed study. In this second detailed study, we were able to do microbiome sequencing.

And we show that nothing's happening in the colon. So the CdtB toxin, the antibodies, they're not changing your microbiome of your colon, they're changing the microbiome of the duodenum, or an ileum, meaning the small intestine. And how it does this is a little complicated. So I will walk you through this.

The rats who got no toxin, their orange, that's normal microbiome of the small bowel, the rat, the green rats are rats who got toxin. But their microbiome is fine, just the

same didn't change. So remember, at the beginning, I said you get Campylobacter. And about one in nine humans develop IBS? Well, the orange is the one in nine humans.

Now it's a little different with rats, because we're giving a really big load of toxins. It's not like food poisoning. It's a little more industrial strength study. So it may not be one in nine and maybe one in three for rats. But the point is that you get the toxin. Some people, they don't get IBS, they just don't get it. And that's what we're trying to emphasize. But then the blue and the purple do get IBS. And the rats are going in two different directions.

There's a group of rats going into a direction of Oh, my overgrowth is going to be E coli, which is a hydrogen producer, and I have I have diarrhea, my overgrowth is going to go in the direction of the sulfa Vibrio, which is a hydrogen sulfide producer.

And I have even more diarrhea, because their microbiome was set up to go in too bad directions. And they either go on one or the other. And that's what we saw on this. I want you to remember that, because we now call these micro types. So the IBS patient or the SIBO. Patients can have diarrhea.

Forget about constipation for a second with diarrhea can end up with one of two micro types hydrogen or hydrogen sulfide. And that's what we see in rats when we give this toxin. And that's exactly what we see in humans with SIBO. Two different micro types for the diarrhea side. And I'll show you that later.

But it's really important to understand that we're getting exactly the same results in rats as we're getting in humans, which is really important and remarkable that we can duplicate like that.

This is a paper that we or a poster we presented at the DW. So it's an extension of this study, the same study. But now we take the rat, small bow and we say what's going on. What are these micro types? What are these micro types doing to you the rat at the tissue level, what are you doing to defend yourself? What are you doing that's causing the illness to be manifest? And what we show is all micro types share differences in gene expression, but circadian rhythm is affected barrier function is affected.

Motility is affected and visceral hypersensitivity is affected a lot of words. But basically what's happening is your gut becomes leaky. That's the gut barrier impairment that's happening.

The motility of the gut is affected, which we already showed you that the motility is affected. And then that's why the overgrowth occurs. And visceral sensitivity, meaning the chemicals that make your nerves feel pain more easily are up. So it's sort of like you have a cut in your skin, and there's bacteria there, you feel pain there, because of that infection are that bacteria, same things happening in the gut.

So if you get a little bit of gas in there, you're going to feel pain more than somebody who has the same amount of gas. So all of these things are not surprising. But it's surprising. It all comes into this model that we're seeing exactly everything we see in IBS, we're seeing manifested by this CdtB toxin, which is brand new, and very, very exciting. putting this all together.

So can markers of CdtB and vinculum predict IBS? So in other words, can you diagnose IBS by measuring these antibodies? And the answer is yes, I'll show you the results. So here's the anti CdtB toxin, or anti CdtB toxin antibody blood tests. So this is the second generation test, I'll show you the difference in a minute.

The second generation test was done because the first generation test was okay. But there's a problem with the way the antibody binds to the protein.

And we figured out a way to make the protein more exposed in a specific way called epitope optimization, so that the antibodies could get to it more easily. And so when we did that, it's better test, it's a much better test for anti vinculin, and for anti CD DVD. And so I'm going to walk you through this.

So you understand this, if you just had a positive anti CdtB, or anti vinculin, your post test probability of having IBS, meaning you have a positive test, what's the chance you now have IBS is 89 and 88%. If both markers are positive 98% chance you have IBS, in terms of diagnostic testing, medical certainty, is 80% or above.

So you want to be above 80%, because that's considered by diagnostic tests, medical certainty. When you develop diagnostic tests, the most important number is likelihood ratio, we're gonna get really deep in the weeds, but it doesn't matter. I'm

going to explain this to you. The likelihood ratio is what determines your post test probability.

The higher this number is, the better the post test probability. So we did develop the first assay, the first one, and this was the number for CTV 5.2. It's now five 6.3 was 2.0 is now 5.3. Here so much, much better. How does that work? Or how does that compare to what's out there?

So let's do a post test probability, the gray bar is medical certainty. And anything below 80% is sub optimal, but can be used but it's suboptimal if you don't have something better. So pain perception is just a way of looking at whether patients have an accelerated or an accentuated response to pain.

That's useless, because the pretest probability is 55%. So that doesn't do anything. There used to be a 34 biomarker panel, which was an algorithmic sort of AI determined panel didn't really get there, bile acids in the stool didn't get there, there was a 10 biomarker panel that was on the market temporarily still, it's not there anymore. 79% visceral hyperalgesia, you put a balloon in the rectum, and you feel pain at a higher at an easier threshold, meaning a lower amount of volume that it gets there.

But it's not great. volatiles in the stool, pretty good part to get this test, the first generation test of CdtB and vinculum, which is still on the market as another other test, which I'm not going to mention, but this is where it sits anti vinculin Here at 60 CdtB. At 80.

The second generation test, the anti vinculin is 87% 89% for CdtB. And if both are positive, it's 98%. So you can see this as a huge improvement. And is the second generation test really is now the gold standard, or at least the best test that we know of currently for the diagnosis of irritable bowel syndrome with diarrhea to diagnose, especially post infectious IBS, so and so here's how it works.

I'm gonna summarize this first half, you've got all these beauty little bacteria in your gut, all sorts of colors and shapes and sizes, and they're just wonderful. They're supposed to be there. Then you get Campylobacter, these green things with a

flagella on the back. And they invade, they produce CdtB toxin, which you get exposed to, you start forming antibodies to CdtB.

First, the anti vinculin comes later. But when the anti vinculin comes, you start to get a breakdown of the nerves, those special little cells I showed you that are reaching out towards each other.

They're not anymore, you get a diminished cleaning wave. And then you get a whole bunch of these characters. And I'm going to talk about these characters when we talk about breath testing next, and that's evil. So now let's go to breath testing, because we need to look at breath testing, and what is the evidence for what breath test you should use, how you should use it, and so forth.

So, ironically, at btw, there was somebody who was a very particular expert and meta analysis did not show this meta analysis, which is the gold standard meta analysis, the most recent meta analysis on breath testing, and IBS. And it's clear that anything above one is significant.

This is the summation of all breath test studies for IBS. And you can see that it's way up there. So breath testing is abnormal in IBS more than it is in healthy controls. People say to me, well, well, what percentage of IBS should be positive on a breath test?

Well, if you just run the numbers on every trial, that's done, it's about 49%. So if you're getting 80% positivity on breath testing, there's something wrong because it shouldn't be that high. It should be, I would argue, between 50 and 60%, of IBS is positive. If you use lactulose, in my experience, and you have an experienced clinician, remember 60% of IBS is this, this pattern of things that I've been talking to you about today. But breath testing is more complicated than we knew.

If you are old, like me, hydrogen was the original gas on breath testing, there was no methane on the breath test, it was only hydrogen. That to me is a useless breath test, because you can't just measure hydrogen, and hydrogen is the fuel for the two other gases, hydrogen sulfide and methane.

So if you don't know the hydrogen sulfide or the methane, you don't know how much hydrogen is being eaten up by other organisms, we now know hydrogen sulfide is

associated with diarrhea more, and methane is associated with constipation more. So you need to know, in my view, all three gasses, and I'm going to provide you evidence for that.

Let's go to the culture studies, because culture was considered the gold standard. So the argument against breath testing was okay, breath testing, great. But it doesn't tell us what's really going on in the gut. I'm going to argue that's not true today, because of some of the new slides I have. But at the time in 2007. culture, culture is the gold standard. Look at culture, culture is more abnormal in IBS than healthy. So yes, there's more SIBO. If you use the correct cut off, which we now prove is correct, I'll show you that data in a moment to tend to the three meaning 1000 bacteria in the gut, or higher, is considered SIBO.

In the small bowel 60% of IBS, D is SIBO. So that's, again, the 60% rule of the sea of IBS-D 60%, we think has zero. So that brings us to the reimagined study, which we're doing at Cedars, which is a very large scale effort to try to determine whether the small bowel microbiome is important to many, many different diseases, we just had a paper on sclera Derma come out.

So if you look at other things we're doing, you will see papers on obesity, you will see papers on a lot of different topics. And because we're finding things, but let's stay focused on Small Intestinal Bacterial Overgrowth.

I've shown this before each ring is getting deeper and deeper into the depths of what bacteria actually is. So if you start in the middle, you can see this is bacteria that is the bacterial kingdom.

And then when you go to the next link, ring is the phylum, so there's Proteobacteria here Firmicutes here if familiar with these terminologies, and then the further out you go, you get down to the Spiess to the genus, and the outer ring is the species you can see we are not naming the species because we don't know what 16 S. So early sequencing data use a 16 s sequencing 16 s sequencing can only get so far to understand the microbiome

[35:00]

But even with this paper in 2020, using 16 s Klebsiella. And this gray one is Escherichia, which is E. Coli. These are not pathogens, these are not bacteria that you eat up in a bad restaurant and you get food poisoning. These are bugs that are in your gut. But they shouldn't be this min, they shouldn't be this high in your gut, look at the normal person.

If you go to Proteobacteria Look how small pro do is Pro to being here. And then you go down to Klebsiella. Is this little tiny layer here and eat? Escherichia is this one here? Look how huge it is in bacterial overgrowth. And I'll show you more details. A lot more interesting than that.

One of the interesting things of that paper, though, is that when we used lactulose breath testing, we were able to get a great correlation, it was the malt. If you use the 20 parts per million at 90 minutes, you have the best sensitivity and specificity against culture against the sequencing results.

And that the hydrogen was coming from actual activation of hydrogen production pathways in the small bowel. So when you're giving lactose, and you're getting a positive breath test, it's from the hydrogen producers that are in the small bowel, not the colon. So those who argue that lactose is checking for colon bacteria, it's not true. This study history proves that our hydrogen is elevated in the small bowel.

Now I'm going to talk a little bit about intestinal myth and antigen overgrowth, and then I'm going to start to put this into a really deep concept to get you to understand how much more we know. But we know that Nathanael brevibacterium, Smithy, is that methane producer that is the culprit in producing methane in the gut.

And when it produces it at a high amount, because there's a lot more of these guys got, you get constipated, you get bloated, we've been shown a lower heart rate and a lot of other properties of methane that are good, but not good in high amounts.

A little bit on the sulfate reducing bacteria or hydrogen sulfur sulfide producers. So they take hydrogen from other bugs like E. coli. And then they converted to hydrogen sulfide.

But it is the hydrogen sulfide that drives the amount of diarrhea you have urgency and pain. And then other factors can come into overproduction of these characters. So we had to develop, we had to work on developing a gas breath test that actually measures all three. And this took years because this is not an easy challenge.

For two reasons, or a lot of reasons. Here's the list, you're not able to transport hydrogen sulfide, hydrogen and methane across the country with existing technologies a number of years ago, especially hydrogen sulfide, because it's so reactive. So it needs a special bag, a special system for transportation, you need to develop an instrument that can measure all three, and in such a way that you're not cross reading other gasses inappropriately.

So you don't want somebody with high hydrogen to show up on the hydrogen sulfide sensor because it reacts with that gas. So you have to orient the sensors in the instrument in a way that doesn't happen. And then you get that you get an accurate, accurate result. And then you have to do science to prove that the test actually works. And that hydrogen sulfide is valuable, and that what cut off should we use?

And so initially it started with five parts per million, it moved to three parts per million, but I'm going to argue that it really should be two parts per million. And you're gonna say Why does he keep changing the cut off for hydrogen sulfide? Well, what you would hate is for me to say, Oh, just use two because I think that's right.

And then later I say, No, no, no, no, it was never two or three. And then a whole bunch of people are getting medications for a presumed hydrogen sulfide positive. When it really wasn't true.

You have to wait for the science to adjust your criteria. You can't make stuff up. And I try very hard not to make things up as we go. Sometimes it takes patience from us and from the viewers to wait for science to tell us what the right thing is to do.

So I know sometimes that frustrates people but you can't just say stuff you have to have some backing and science. So this was the original study where we used the five part per million cut off; these were diarrhea patients, what we call functional diarrhea, not the IBS or IBS-D. These were fun for multiple patients.

And you can see that hydrogen sulfide was way up here as compared to the healthy and the constipation patients. And that hydrogen sulfide was proportional to the amount of diarrhea. But I'm not going to spend a lot of time on this because I have a lot better data now.

So this is a study where it's a double blind randomized control trial for a drug that we're working on for diarrhea, IBS, which can't talk about, and constipation, IBS, a different trial, a double blind, randomized, controlled trial, in both studies at the baseline, we did lactulose breath testing with three gasses.

So this is really important, because this study for the first time is showing that yeah, that the first time, we're showing that a breath test, using three gasses, and specifically having to use lactulose, correlates with the gut bacteria at a microscopic level. So the breath test is, in fact, telling us very clearly what's going on in terms of the proportion of bacteria in the gut that are causing problems.

So this is really important because it emphasizes lactulose is an important substrate. And it emphasizes that the three gas breath test is the only breath test that is validated against the microbiome in this detail. So let's go and get cut into it. So if you look at methane, and you're a dire IBS-D patient, you're the blue line here, you don't have methane, the D patients almost never have methane, it's and we didn't select patients for SIBO.

This was an IBS-D trial. Here, you can see that not everybody was seen had methane, but the ones that did this was the methane level. So it was quite high, and it started high. We always knew that with methane, methane either there or not there, it doesn't necessarily get all that much higher with electroless. Hydrogen, on the other hand, is the blue line here again, IBS-D.

Look at the hydrogen on average, and a D patient by 90 minutes, it's over 20. Now, of course, there might be some below there. Remember, we said 60%. But on average, the majority of the patients already reached the threshold that they really truly have SIBO. Look at the methane people.

The methane needs hydrogen to make methane. It has to have hydrogen to make methane. And look at the hydrogen values in the methane group, lower than even the non methane constipated patients.

Why am I saying that? Because when you're measuring methane, your hydrogen is lower because the hydrogen is being eaten to make methane. So you can't measure hydrogen without knowing nothing. And I will argue that you can't measure hydrogen without knowing hydrogen sulfide.

Also, same problem. Here the hydrogen sulfide levels are higher in IBS, D versus the other two groups. Here's where we're now getting really exciting. So the new three gas breath test using lactulose as the substrate, we can correlate directly with the amount of M Smith ei in the gut. And you can see these are the correlations, these are the P values.

So the breath test is validated by the fact that yeah, we're actually measuring methane on the breath. Yeah, we're actually correlating with the amount of myth antigens in the gut. And yeah, we are correlating with constipation. So it validates the breath test more.

And these are the correlations, we're able to correlate the methane, here's the methane, correlating with the antigens, two types of pathogens in the gut, again, proving this correlation. I'm not going to get into too much detail, except I'm going to say one thing about this, these two characters, Kristin, cynnal, ACA and Ruminococcus.

ACA are the gut bugs that produce the hydrogen for the patients with methane. It's not the E. coli and Klebsiella. This is the constipation side of the story that's really unfolding very quickly now. But I'm not going to get into all those details. In the hydrogen sulfide group.

The hydrogen sulfide on the breath test correlates with the hydrogen sulfide producing organisms in the gut. Again, validating that what we're seeing on the breath test. Let me just emphasize very clearly, the lactulose is driving hydrogen sulfide production.

The hydrogen sulfide we're seeing on the breath test is being measured accurately to the point where we're able to correlate with actual microbes in the gut. So the bags get sent five days, whatever it takes to get to the lab. And still the gasses correlate perfectly or very well I should see statistically with the, with the microbiome never been shown for a breath test. So this is a really important study that was published just before this before New Year's.

And that the breath test is correlating the hydrogen sulfide level is correlating with fucile bacterium, which is a hydrogen sulfide producer.

Okay, I'm going to skip this because it's now getting too deep, and I'm going to lose you all. But again, the breath test using the three gas breath test, methane correlates with all the stuff that makes methane. And on the right, the hydrogen sulfide correlates with all the stuff that makes hydrogen sulfide in the gut, all the way to the pathway level.

So now with this three gas breath test we can see an eye and correlate it with the gut bacteria, three distinct micro types. And so this is the all new hydrogen micro type, the sulfur or hydrogen sulfide micro type, and then the Matthias antigen or methane micro type, which drives constipation. So constipation here, diarrhea for these two groups. So let's talk about breath testing.

Now, as we wrap up, getting closer to the end, I do have a few more tidbits for you. So no, this is a long presentation. But bear with me. These are the three consensus we did the first consensus on breath testing 2018. Here are the follow ons.

There's most of the world who's had consent part of these consensus statements agree with the criteria for SIBO. Most of the world agrees with the substrates and dosing. And most of the world agrees that SIBO and IBS are interrelated now.

So we've come a long way from 1996. But here's the newest stuff. So now we're trying to get to the point where we're able to say okay, now we know who exactly is causing all this hydrogen. We know it's Escherichia, we know it's Klebsiella.

But we need to know more, we need to know exactly who they are. And this is culturing the small bowel. So some centers in the United States culture, the small

bowel, and they take this anger and this anger and they pull it together. And they say, if it's over this, you got overgrowth, this regard does not work.

Look how many patients we have, in this study, a huge number of patients don't work. It does not, there's no difference in diversity of the microbiome using the blood agar. But look what happens when you use MacConkey Agar.

And you get to greater than 10 to the three, already, you're seeing a tipping point in the microbiome. So anything over 1000 on this growth media, or age is overgrowth. This is super interesting.

This was just presented a couple of days ago. This is your network of your microbiome, the network is all these lines connecting dots are all the microbes in your gut all communicating with each other in the sense that, hey, if I'm here, you should be here. And we're like a family. We got a plumber here, we got a doctor here, we got a lawyer here, we got a sanitation worker, etc.

The city is in harmony, because there's lots of dots and lots of lines. That's a good healthy microbiome. But the microbiome starts to break apart when you get to over that 1000 mark on that growth media. And when you get to over 100,000 of those bad bacteria. It breaks down completely, nothing's connected.

There's only a few dots, a few lines and the microbiome really starts to just fall apart. We also presented at DW them with antigens and they are everywhere. So the point is the biggest group is still the MacDonnell brevibacterium ACA, which is McDonnell breva Baxter smithy AI, which I've told you about, and they are in the duodenal and they are in the stool.

So they are , that's why it's called IMO, intestinal advantage and overgrowth, because it's not just in the small bowel, it's in the stool also at almost equal amounts. And then I want to show you something really sort of interesting and then one more thing interesting after that because I think this is just getting so deep.

This is an app that we use to look at stools so patients take a picture of their stool before wiping and putting paper in the toilet. And we're able to see exactly what the stool look like in the AI in the in the app calculates this Bristol score, the edge fuzziness, fragmentation and other factors and when you have methane, your Bristol

stool score is lower, your edge fuzziness is less meaning the stool is more smooth and tight like like, like balls and fragments.

And and and you have less fragmentation, meaning you don't have like little bits and bits and bits and bits of loose stool.

Look what happens with hydrogen sulfide. And this is really important. So if your hydrogen sulfide is positive, you have more stool volume. Compared to a hydrogen positive patient, when your hydrogen sulfide is there, you have more stool along with your negative for all three gasses, the differences even greater.

If your hydrogen sulfide is greater than two, that's when the volume starts going up. So it may be a better cut off. And that's where we're heading and continuing to learn more science around hydrogen sulfide. Alright, and finally, remember, I showed you this circle, and I showed you that SIBO is really important. Now with shotgun sequencing, we can figure it out all the way down to the strain level, what bacteria are present.

So similar circle, except now we got the outer ring, which is here. Okay, so what I'm going to do is I'm going to continue this and show you, this is SIBO. This is what normal people have for this group of bacteria called Proteobacteria. This is normal here on this side, tiny amount, tiny piece of the pie, more than 50% of your entire microbiome is now Proteobacteria.

But no, it's more than that. Look at this 18% of your entire microbiome is one species Klebsiella pneumonia. And another 28% is just E coli, which is this one here, this gray one here.

And now we know all the strains of these organisms that are part of SIBO and all the bad things that they can do. And so when we know the strains in the species, we can direct our treatments even more better.

And these species and strains that we identified for SIBO are correlating with bloating, gas, abdominal pain, diarrhea, urgency, etc, for both sides, both Klebsiella and ecoli. And they are together in most cases. So we now know the exact strains of bacteria that cause SIBO.

But can you imagine your beautiful microbiome of 500 different bacteria boiling down to two species taking up Almost 50% Almost half of everything there and that SIBO nothing in the reimagined study looks like this.

This is a very, very remarkable apocalypse of your microbiome. And and then the last thing I'm gonna show you is this, this because this really kind of emphasizes the point. So because you have these E coli and Klebsiella pneumonia in your small bowel, what happens is these two guys, these two characters are amazing fermenters.

So they jack up your ability to digest sugars, to new highs. So people say, Well, I just ate and then I'm already getting gassy. The small bowel is so jacked up to ferment because of the high numbers of these very intense fermenters that you get these regulations like 63 times higher amounts of glucose degradation.

Don't be fooled by that. That doesn't mean a glucose breath test is better. I'm saying carbohydrate digestion is all accentuated hydrogen sulfide production. And then there's some of these other pathways, which I won't get into today, because it really is going to be too complicated, but super interesting pathways that you will hear more and more from me about in the coming year or two.

Again, I'm showing us these networks, this is what happens with E. Coli. When it goes to this level, it's more broken when it goes to this level, higher level it's even more broken Klebsiella is even more destructive, you can see that the network really sort of just starts to fall apart as Klebsiella goes up. And then finally, these are the pathways in humans.

Again, strong association with motility genes with barrier function. So these bugs and the CdtB toxin and everything on top of each other are changing your barrier function, changing your histamine secretion, changing your inflammatory response, changing your motility and causing further worsening of the situation. So, three gasses is what we measure either in hydrogen sulfide and methane.

This is the physiologic sequence, which we built greater evidence on at all levels. Since the last time I've spoken to you. We treat IBS based on this study.

Rifaximin is FDA approved for irritable bowel syndrome. But if your breath test is positive, you're more likely to respond to Rifaximin, 56 versus 44. And if you make that

abnormal breath test normal, those patients respond 76% of the time. In methane, we give Rifaximin in Neomycin, based on this double blind study, that's what we do. It's not FDA approved like that.

But if you're methane, this study is something to lean on for treating raw methane positive. We don't have a new thing for hydrogen sulfide yet. But things are coming. Let's say that. So this is what I do in my clinic based on everything I've told you about chronic diarrhea, mixed.

I do the antibody measurements because it helps the patient and helps me understand what's going on. I do the three gas breath tests. It's hydrogen, I give her facts to summon if it's hydrogen sulfide now greater than two for me in my clinic, I give bismuth and Rifaximin. And that's worked really well for some patients.

And ironically, some of the patients with hydrogen sulfide a year later, they don't relapse like the ones with hydrogen constipation, I don't need to measure these antibodies, because that's not part of the mechanism there. But I did the three gas breath tests.

Because there are patients who have all three gasses seen this often enough, methane always wins. So you will be constipated if you have nothing. But what you don't want is to get the methane down and not treat the hydrogen sulfide and flip them to diarrhea.

So I still want to know all three gasses and I use Rifaximin in Neomycin, or sub the Neomycin with metronidazole, which seems in clinical practice to be working just as well. So three more slides. I started with this slide that this is where we were with IBS in 1996. This is where we are now with the microbiome. I've shown you a lot of this detail. I'm not going to go through this slide, but a lot has happened.

So in conclusion, IBS is commonly a small bowel microbiome disease. SIBO is a very important contributor to that. We now know the characters E coli Klebsiella pneumonia, and that they produce the hydrogen and getting rid of that hydrogen getting rid of those bacteria makes you better it makes the patient better.

M smithy IR myth antigens are responsible for the methane in the gut, and they constipate getting rid of methane makes the constipation better. Hydrogen Sulfide is

really important to further understand that this third dimension of the microbiome, the breath test, the three gas breath test is now validated, the whole system is validated against sequencing of the gut.

So what you see on the breath test is what we're seeing in the gut in the microbiome. So that's super important. And everything we've done uses lactulose. So the lactulose, and the system of three gasses, is what's being validated here.

And this second generation antibody test is far better than the first generation and is more accurate and unimportant. So we're understanding IVs for the first time in new ways, and I think it's going to change how we treat this disease. So I'm going to stop there and hopefully, it wasn't too long.

[58:41]

Shivan Sarna: Going as far as we're concerned,

Dr. Siebecker: Oh my God, not too long at all. I'm like, Don't skip over that slide. Talk more. Fabulous. That's amazing. Congratulations

Shivan Sarna: That's amazing. Congratulations on all the progress seriously.

Dr. Pimentel: Yeah, a lot of progress this year. So I'm really, really excited for patients.

Dr. Siebecker: Thank you so much for all your work that you do every year on behalf of all of us. This is incredible.

Shivan Sarna: And your advocacy by actually speaking on podcasts and being with us for our sessions, we really appreciate it. And we're thrilled to get the word out to people because this is exciting. We're not used to having a condition that we get to watch the research emerge and know that there's so much hope coming within our lifetime. This is very motivational for us to stay the course and we are very appreciative, so send our best to the team.

Dr. Siebecker: Okay, I'd love to start with something slightly off topic from the research that's new that you presented because so many people are thinking about this now. In the last year, there has been huge publication or awareness and increased use of semaglutide and similar drugs - this is sold as Wegovy, Ozempic,

and Rybelsus. And we know that one of the mechanisms or actions of this drug is to slow stomach emptying slowly, and they basically slow upper GI motility. And so I have two questions. First, should people be concerned that this could be a cause of SIBO by slowing the migrating motor complex?

Dr. Pimentel: All these drugs, including Mounjaro™ are commonly used now. And it actually affects a lot of what we do. For example, if you're on one of these medications, and you do a breath test, it's a flatline because the lactulose never leaves the stomach, and the stomach just doesn't empty. So it's not that it slows the cleaning waves, it slows everything. So it's more problematic than that.

Now, we don't have a lot of details on if you're on one of these medications. Are you getting more SIBO? Or not? Or are you going to precipitate SIBO? We don't know. I mean, it's really early days on this, but one would imagine anything that slows the gut down leads to bacterial buildup, there's no doubt about that, in my mind. What that does in the long run, we don't quite know yet. But you're right, it's a big problem. Well, I guess obesity is a big problem. And solving obesity. And these medications actually working is actually a good thing. But there's always a yin and a yang with everything we do in medicine, so you can solve one problem only leading to another.

Another example of that is these new anti-cancer drugs. They're amazing. But they cause type one diabetes in some patients because they destroy your islet cells. So we're seeing as surgence of diabetes in a lot of patients from these anti cancer drugs, which are life saving. So, it's, you're beating away one devil and you're getting another devil and you have to decide which devil is worse. Cancer is obviously a bad example, because it kills you. And diabetes can be managed, so you take those risks, but that this is what we do in medicine, we have to put everything on a balance

Dr. Siebecker: Thank you. My second question is, what about people who already have SIBO? Who wants to take this or start taking it? Have you seen any examples or any concerns there that are going to make their symptoms worse because it's going to slow motility more?

Dr. Pimentel: Yeah, I have a few patients, but very, very few. Because I think they know that slowing the gut down causes them to be more bloated, but it's always more complicated than you think because what those drugs force you to do is eat less,

you eat less, you ferment less, you have less substrate for the bacteria. So maybe on balance, it doesn't do much. It doesn't make it worse. It doesn't make it better. It keeps it about the same. I don't know. We need to study it because almost everybody's going to be on these medications. Judging from what I'm seeing in the news media, even people who are not so obese want to lose a few pounds. They're on these medications now, too.

Dr. Siebecker: Thank you. And Shivan, did you want to say anything more about that?

Shivan Sarna: I have personal experience with it, because I have it on semaglutide Because of my blood sugar. And I'm half Indian from India, which I know you're familiar with Dr. Patel, and, they're in my father died of a heart attack and definitely had insulin issues. Skinny arms and legs on a tummy. Right? So that's very typical for Southeast Asians. And I've never puked so much in my life, because the stomach doesn't empty. And so has it made my SIBO worse if I was feeling positive at the time. It hasn't. But like you're saying there are other implications to it, so the jury's still out.

Dr. Pimentel: It's been interesting back up, it's not feeding the bacteria.

Shivan Sarna: There you go. There's a positive,

Dr. Pimentel: A lot of positives, but what I mean, this is the problem, you're gonna be eating less because of these drugs. And so maybe they get less food and therefore it doesn't change anything, but I'm just speculating. We don't have any data yet.

Dr. Siebecker: Okay, thanks so much, Dr. Pimentel. That's been on my mind so much since everyone's been exploding with that drug. This is interesting. I was so taken with your explanation of the likelihood ratio for your second generation, CdtB test. I was thinking about the fact that other than your first generation test, there are two other versions of that test on the market, copycat labs. And there are a lot of functional medicine practitioners and naturopaths. who use those other labs, because they order stool tests or something else from those labs. And so then they just are using those labs for their CdtB testing. Do we know anything about the likelihood ratios and the validation of those other laboratories.

Dr. Pimentel: None of them are using epitope optimization because they didn't even know what that means. It's an internal process that occurs with the second

generation test. Basically, they're all first generation technologies. You can see what you get is what you get. And it's not that great, but it's not that great. It's not as good as the second generation. So it doesn't make sense. I mean, if I was a patient, and I'm paying the same price for two tests, you get the one that works better, I guess, is how I see it. And the more accurate it is, the better it is, the more you're likely to do the right thing for the patient and save money, which is what I said at the beginning. The more accurate your test, the more money you save in health care period. Everybody knows this, so we tried to improve it to get it more accurate, because we knew it wasn't good enough. I think it's good enough now, because we can't really improve on it.

Dr. Siebecker: Okay, great, thanks. Just clarifying it sounds like you're using two parts per million now for your criteria for positive for hydrogen sulfide, will we see a change coming officially?

Dr. Pimentel: I think based on the newest data, they're going to adjust the report to say, based on new evidence, there is accumulating evidence that two might be the cutoff, so use it in your judgment in your clinical practice. In my clinical practice it will be the new cut off for me, that's what I'll be treating. I feel competent enough, but we were not done. We're still studying this, there's more to be done to define it better. To define new treatments. We're always about two years ahead of the slides I show here, so we know a lot more coming. There's exciting things coming, I'm very optimistic.

Dr. Siebecker: I know Shivan always tries to get it out of you and you never crack.

Dr. Pimentel: That's why I said it now. So you can avoid it.

Dr. Siebecker: Okay, another one is so exciting about figuring out the species and strains for the Klebsiella. Also I just want to say how incredible this is. I love the way you started the presentation, bringing us back to how it was and how we're having troubles with the acceptance here and the comparison to Crohn's, IBS and SIBO. And it's really getting harder and harder for people to maintain that when you're getting down to the species and strain level of exactly which bacteria are causing the problem. That's amazing.

I was wondering if you were talking in one of the abstracts about how you can have an unspecified strain of Enterobacter has been found as one of the culprits. That's new, isn't it?

Dr. Pimentel: Oh, I see what you're saying, an unspecified string vendor. But yeah, and then one of the abstracts?

Dr. Siebecker: Yes, one of the abstracts is like there's, there's E. coli, there's the two strains are species of Klebsiella. And then an unidentified enterobacter. In the previous work you've had done. You had said you found a little bit of aeromonas. And now you're saying enterobacter. I was wondering is aeromonas underneath the heading of enterobacter or are these just two different things you found?

Dr. Pimentel: Remember, 16S measures ribosomal RNA sequences. And so it the ribosomal RNA of different bacteria have different sequences. When we do that there's a lot of overlap between different bacteria a lot and so when the computer goes through the algorithm is okay, then what does this line up with? Who does this line up with? Who does this sequence line up with? They make estimates and so when we say with 16, is that it is Aeromonas or Enterobacter, or Escherichia? It's an estimate, we're sequencing the DNA from the central core of the bacteria. And if you sequence long enough and enough of it then you know exactly who that organism is, with 99% estimation. And so what we could have called aeromonas before with a rough estimate, we now call Escherichia or something else, we'd have to go back and compare the sequences and why it said aeromonas. And now it's not so important anymore because we now know the truth. The truth is shotgun. And so let's move forward with the truth. Forget about aeromonas for now. That is how I see it because we're just wasting time we need to get to treatments now. We have the good answers, not not the old answers. It was always Escherichia and Klebsiella. We knew that even back then, we just didn't know the details down to the species and strain. That continues to hold true.

Dr. Siebecker: Okay, very, very helpful. I also noticed, I think it was one of the abstracts, the one on methanogens, at least one of the ones on methanogens. It looked like there were different syntropes for methanogens between the duodenum and the stool. What's that so?

Shivan Sarna: What is a syntrope?

Dr. Pimentel: A syntrope is like your buddy and so you need a buddy to produce hydrogen to give you the hydrogen to make the methane. We're in the early days of understanding Dr. Allison Siebecker so I don't want to hang my hat on the syntrope thing yet, but it looks like in the colon the christensenellaceae and Ruminococcusia holds true. In the small bowel it may be other syntropes because Christensenella and Ruminococcusia are not common in the small bowel. And then the other thing you may have noticed is that Methanomassiliicoccus, that bug is a methanogen and it fights with the Methanobrevibacter, so the higher the Methanobrevibacter the lower the Methanomassiliicoccus, the higher the Methanomassiliicoccus is the lower the Methanobrevibacter.

They're like two competing gangs trying to win the methane day, but for the most part, it's M. smithii 80-90% of the time, but the other ones are trying to muscle in, so it's like Game of Thrones, right? We have these different families competing and are yelling at each other to try and win dominance in the data.

Dr. Siebecker: Okay, great. Amazing information about the genes that are affected in SIBO, you presented that today. And I just was hoping you could clarify a little bit because you were talking about these genes, leaky gut, histamine circadian rhythm, all these things that seem to have an effect. These genes get altered from the SIBO, but there was also the motility piece, and you call that out a bit. We know that the motility gets slowed for SIBO to occur, but then it sounds like once the SIBO is there the motility is further affected. Could you clarify?

Dr. Pimentel: Yeah, so this is a part I can't clarify. And not because I can't talk about it. It's because we haven't done the clarification yet, so we know that CdtB leads to antibodies that leads to slow motility that does affect barrier function in all the things that on that CdtB poster I showed you. A lot of the things we're seeing in the end of the game, the CdtB did it affect the barrier function, it affected motility, affected visceral hypersensitivity. And then when we're seeing the final result, which is that all this elevates E coli and Klebsiella. We also see the same signals. So we're trying to figure out, all these signals are screwed up. But is it the E coli Klebsiella? Or is it the CdtB that screwed it up? And which chicken or egg are related to all these findings

and in that part is not exactly clear. because with the CdtB, you're getting these elevations in E. coli and Klebsiella. We're trying to dissect out, is it the SIBO that's causing some of these pathways? Is it the CdtB antibodies? Which are causing some of these pathways? Or is it both? And what are what's causing what? It's still a puzzle to be sorted out.

Dr. Siebecker: This is the semester I teach at the college and I shared the new research on genes the moment it came out, last week, and that was their question, chicken or egg? And I figured you were trying to figure it out?

Dr. Pimentel: We are working on it. But it's a complicated question because it's almost impossible to separate the two, so what we would have to do is take the animals who are CdtB positive, treat their SIBO, get the E. coli and Klebsiella down and see if these expression markers recover, or if they're still screwed up. That's a study we have not done, but that is the study that we need to do to prove that. A hard study to do in humans because it's a lot of aspirants, and biopsies? It's just too expensive and cumbersome for patients to go through.

Dr. Siebecker: My last question is, were there any other abstracts or presentations at DDW this year that you were particularly excited about?

Dr. Pimentel: I can tell you what was super exciting at DDW, for the first time in history, there was an entire session of multiple lectures on small bowel microbiome. We've never had that, it's always been stool, stool, stool, so there's an entire section now dedicated to small intestinal microbiome and people are finally working in that area. That's the goal. This isn't about me, this is about patience. And I don't care who finds the final result that helps the patient. It's just let's go people. Let's get this done.

Let's help some patients. So I'm super excited to see other people now interested in that and, and they're saying things, and I'm listening to them talking. And they're saying things and I'm like, Well, I can't believe somebody else said that.

The speaker who introduced the whole session said, we know we haven't found too much in the colon, and stool but in the small bowel, it's a large surface areas and absorbing surface. And so bacteria in the small bowel can affect the human more

than maybe the colon. I'm like, huh? I said that for a long time. I'm glad to see somebody else saying that. And so it's an exciting transition.

Dr. Siebecker: Is very exciting.

Shivan Sarna: That is very exciting. Good. I'm glad just personally for you.

[1:18:07]

Dr. Pimentel: I'm doing stuff otherwise, no. Part of medicine is part of medicine if you gotta believe stuff, but validated. Right? So it can't just be one center publishing an area, it's important that other people say okay, like the meta analysis on breath testing.

Almost all the studies weren't us, one or two of them were but the rest of them were other centers, super important that everybody's getting the same result in the same signal. There were more studies on methane and constipation, so I think methane and constipation is a foregone conclusion.

There are very few people who disagree with that now, because other people have proven this to be true. So, we keep moving forward, and other people replicate it and or prove it's right or wrong. If they prove it's wrong, then we have to figure out what went wrong and correct it. But science, you take what falls out of science and you publish it, and then other people either verify it, or we make adjustments over time.

Shivan Sarna: Fantastic. All right, I have questions. Dr. Pimentel, I wanted to just have you say it out loud for anyone who missed it - about what happens once SIBO / IMO is resolved to the microbiome, that the microbiome restores back to harmony.

Dr. Pimentel: We haven't published this, but we've seen in the reimagined dataset that of patients who had SIBO, who were treated, their microbiome completely comes back. Again, it's the weeds in the garden analogy, you pull the weeds out, and then the vegetables grow much better. And I think that's true.

And we don't see Rifaximin resistance genes in the microbiome, which is amazing. We see this microbiome recovery after getting rid of the bullies. So I'm not sure Rifaximin is, people worry about antibiotics, antibiotics, any bugs perfection, it's not

quite like that it does something special. At least that's what we're seeing us, we need to continue to monitor things and watch, but that's what I'm seeing so far.

Shivan Sarna: So that is a really big message of hope for everyone who still has those questions about their microbiome. And I hope it's also motivating to everyone who's listening to this to like, really go for it and get those treatments, because the rosacea can improve, right, the restless leg, all of these other associations you were talking about with the low heart rate? I find that so interesting. Why is there a relationship between people with methane and lower heart rate?

Dr. Pimentel: Well, so what we used to use to put people to sleep to do surgery, carbon tetrachloride. A carbon tetrachloride is a carbon with four chlorine molecules around it. We have a molecule called methane, which is a carbon with four hydrogens around it. So it's just a substituted hydrocarbon, carbon tetrachloride.

Now we don't use carbon tetrachloride anymore. We use Eisele, fluorine, which is still a substituted carbon molecule. And these gasses, these anesthetic gasses are effective, they affect your blood pressure, they affect your pulse rate when you're under anesthesia. And methane has, I don't want to say anesthetic effects, but it has groggy effects, because it's similar to all these anesthetic gasses.

It's like the canary in the coal mine when the methane goes up, the canary falls asleep and then you know that there is too much methane in the coal mine. That is, maybe, why patients get brain fog and methane. And we just need to understand the methane effects more. Lower heart rate. Interesting. It's fascinating.

Shivan Sarna: So it'd be easy to extrapolate that that can lead to fatigue, right? That kind of feeling of lethargy.

Dr. Pimentel: Well, if it blocks your heart rate, or blocks the heart rate from going up appropriately or slows the response, so you can't can't exercise as vigorously because you can't get that response at heart rate. We're guessing here, we're just...shooting the breeze because we don't have data yet. But there are a lot of potential implications of a lower heart rate and what that means, when I say it's lower, we're talking about three beats per minute lower, but over a lifetime that's a lot of beats.

Shivan Sarna: I'm gonna go to fungus land now. I heard that you guys did start talking a little bit about the fungal overgrowth. Can you just elaborate on that a little bit.

Dr. Pimentel: I didn't put that slide in, but we actually for the first time sequenced fungus in the small bowel. If it's over 1000 in the gut, it's associated with symptoms. And now it doesn't happen often. So it's not like SIBO, where it's common. It's uncommon, but when it is present, we said two things in the presentation. We said that if it's over 1000, you do get symptoms. If it's usually Candida. And we're trying to isolate the specific species and strain and all the stuff that we've been doing with the SIBO and now we have the tools to do it, so it'll happen faster. It's there, but not.

Shivan Sarna: That's exciting. Okay. And then. There's been a lot of buzz, I've been following you on Twitter about the non caloric sweeteners and how they affect the microbiome.

Dr. Pimentel: Yeah, a lot of new stuff. So we've been saying in our low fermentation diet, that aspartame is fine, it's a protein, so it's not a carbohydrate, and all the other ones are carbohydrates, and maybe that's bad for SIBO. And so we finally looked at that question. In the reimagined study, people who self declare that they take aspartame self declare that they take these other sweeteners, and the other sweeteners we saw over 70 different changes in the microbiome with the car carbohydrates, sweeteners. We didn't see things like that with aspartame. So yeah, the other sweeteners are doing substantial things to your microbiome. I can't say good or bad. But as you can see, when you have SIBO, as I said, you are jacked up to ferment sugars. And if you put nondigestible sugars in there, and you have that heightened ability to digest them, you're gonna get more bloated. And so that's a bad thing, which reinforces what we've been saying, but with really good hard science.

Shivan Sarna: I'm literally trying to find the name brand for the aspartame because I have never used it.

Dr. PimenteL: NutraSweet.

Shivan Sarna: When people do clear SIBO back to a little bit more motivation for taking the treatments on. What other symptoms do you see? As far as people's symptoms go away over the bloating, they get regular regulation of their bowel movements. And, we talked with a couple of people and Allison, I've talked about this a lot that a lot of times food intolerances disappear, fructose can then be consumed more comfortably. What else do you see is like other than people like getting their lives back. But any other comments on that?

Dr. Pimentel: Well, I do see clearing of brain fog and other things as well. So there's a number of things that seem to get better, such as allergy symptoms getting better in some patients, not all patients, and not all patients have allergy symptoms. So it's just like the rosacea thing, where not everybody with SIBO has rosacea. But maybe it gets better in some of these individuals.

We see a lot of very interesting odd things that happened. And they're not just one offs. They're fairly routinely seen. Remember, these bacteria create an inflammatory condition, they really heighten your immune system. And so if you have immune disease, it's possible that it could flare.

Shivan Sarna: Two more questions before we wrap: if someone had a positive CtvB, from IBS smart, and they have methane on a SIBO breath test, would that indicate or give you a clue that it's actually they have enough hydrogen to be feeding the methane? You talked about that a little bit? I just wanted to clarify.

Dr. Pimentel: That is a little tricky, right? Because I don't routinely measure the antibodies in methane, so don't quote me on the numbers. If I remember correctly, the antibodies to CdtB and or vinculin are about here and healthy. They're here. The prevalence is here for IBS-D. And for IBS-C, it's here. I'm not giving exact numbers.

I remember the number is 56% for the CdtB and vinculin for IBS-C. I don't remember the other two, but there is a signal, a statistical signal for methane. I just feel like if only one in four or five of methane people are positive, you have to spend money on five people to get one positive. I feel like that's not cost effective, so I tend to not do it. But then again, brings up Dr. Allison Siebecker's question, these methanogens and their syntropes are different if it's small bowel methane, or it's colonic methane. And so if you get a bunch of Klebsiella and E. coli going up in the small bowel giving fuel

to the methanogens in the small bowel, maybe you can become methane positive in this scheme. But, again, these are things we need to figure out. It's a complicated system to figure it out.

Shivan Sarna: And as far as the vaginal microbiome, do you feel like that could be impacting the small intestinal microbiome and the large intestinal microbiome due to their proximity or the ability for microbiome bacteria just to move around your body?

Dr. Pimentel: Generally speaking, the entry for vaginal orifice and the anal canal are close in proximity. So you're more likely to see stool microbes sort of migrate into that area. Rather than there'll be sort of bugs going through the bloodstream or crossing the tissues and jumping into that area, so I think it's more than the latter. When we have SIBO, it's possible there's more E. coli around and E. coli is a common contaminant for example in urine infections, especially in women. So is that where they're coming from? Hard to know.

Shivan Sarna: I do have one comment, also. Thank you for that. The first slide, which was talking about back in the 90s, where people were thinking that it was a disease of hysterical women and all of that. And I saw on the left hand side of the slide, stress, trauma, things like that. There's still a contingency of people who and I understand why they're thinking that, well, I got really stressed when I got SIBO. You've talked about military examples in the past. Could you share that one more time for people who are just hearing it? Or as a reminder for the first time?

Dr. Pimentel: Yeah, so my good, good colleague and friend, Dr. Mark Riddle used to be at the Research Institute for the US military in Silver Spring, actually. What they found was that if you were in deployment, they looked at the factors in deployment, because people, these people were coming back from deployment in Iraq and Afghanistan, they were coming back with IBS. So what in deployment was the highest risk factor? Well, it turned out it wasn't stress, it wasn't whether you shot a gun, witnessed human death, or suffering, or yourself was injured, or maimed or or had some kind of traumatic event. It was food poisoning, if you got food poisoning in combat. So it was the first example of looking at a person going through time, what they experienced, and why IBS developed. And it was food poisoning.

And the cause wasn't all these stressful events. And I can tell you, in the US, in general, we're not going to explain the experienced type of stress that somebody in combat military operations might experience. That's extreme And so if that doesn't do it, how is it that my boss got mad at me today? And I'm stressed, by itself, not going to do it. We need to do more studies on stress and its effect on the gut. We know stress affects the gut, we know it changes the migrating motor complex. Does it make it worse? Yes. Is it the cause of IBS? I would argue that we have evidence that it's probably not the cause of IBS, it is a modifying factor.

Shivan Sarna: Right? Okay. Thank you so much for saying that because that gives a lot of clarity. People get in fights in the Facebook group over this. It's a contributing factor.

Dr. Pimentel: Let's say your antibodies are just me putting it into the perspective of what I've shown you, maybe your antibodies are borderline, and then you got stress as an additional factor, which is reducing your cleaning waves just that much more. And then you say, oh, it's the stress, but no. You're at your tipping point. And then you tip it over with a little bit of stress, which makes the motility worse. So I can understand why people will actually feel and say that physiologically, is what's happening. And yes, it tips you over. But I don't think that's the mechanism of IBS. I think it's a cofactor.

Dr. Siebecker: And also, I think no one would argue with the idea that if you have IBS or SIBO, and you do stress control measures, you decrease your stress, you will feel better all around and your digestive symptoms may improve some. Stress as you say it's a modifier, but will it cure? That's going to be rare.

Dr. Pimentel: If you're doing your favorite thing, you say you have pain in your leg, and you're doing your favorite thing. You forget about the pain for a while. Let's say you're playing the piano and you just get into the zone of the piano and you forget about the pain in your leg that you have. I mean, that's distraction techniques, and or mindfulness or whatever you want to call it. It's great. But it does not change the physiology, or what's going on in your body. It's just trying to get you to cope. So it's something that allows you to live your life with illness.

What we're talking about today is how to cure the illness. You don't have to do all of those things to try and live with it. Yes, there are important things to help you live with it, but why should you live with it.

Shivan Sarna: Great question. Great question. I think we should wrap up on that. There's so much hope. We hope that you all have taken this information and will watch this recording over and over again. So you can really absorb it. Talk to your doctors, talk to your clinicians, your practitioners absorb the information so that you can turn this learning into your thinking and that you can support your meta called practitioners.

If they have it, feel free to share the recording with them. They need it. And we have lots of practitioners who watch these, too. Thank you all for your commitment to ongoing learning. Yes, cheers to you. Dr. Pimentel, thank you so much for joining us. We can't wait to do it again. And we wish you Godspeed. Thank you, Dr. Siebecker, as always fantastic questions, a great co host.

Dr. Siebecker: Thank you so much, Dr. Pimentel.

Dr. Pimentel: Great talking to you. Always good questions. Thank you.