Host: Michael Roesslein:

All right. It looks like we're live. I see everybody piling in. I will be waiting for Kiran. Good evening or good morning, or whatever time you're in. Good afternoon. It is night time here. Let me see. All right. I actually just got done recording a masterclass presentation with Brendan Vermeire who presented at your recent event in Colorado, I believe. Right?

Guest: Kiran Krishnan:

He did, yeah. That's awesome.

Host: Michael Roesslein:

He said to say hello. He was talking about toxins and neuroinflammation with his beautifully designed and graphically animated slides, which were very impressive.

Guest: Kiran Krishnan:

Yeah. The LPS, I'm sure he brought up.

Host: Michael Roesslein:

He did bring up LPS, and that's largely what we're going to talk about today too. And this webinar, I had one agenda for it when we originally booked it, and then we recorded the masterclass presentation. For those who don't know, we are going to be launching or airing a new masterclass event in February.

And so I'm recording all of those now. We recorded Kiran's... I don't know, I've lost track of days, but a couple weeks ago. He gave a very in depth excellent presentation on endotoxemia and lipopolysaccharide and all the different disease states and processes and problems and symptoms caused by endotoxemia. I was so blown away that I decided to scrap what we were going to do on a webinar, and I asked them to come in.

We're not going to get to the same depth. I mean, that was an hour long presentation. Today, we're going to be a little bit more surface level and main points and just really get it out there because this is something I felt that everybody needs to know and understand as soon as possible.

I mean, I've been listening to you teach for a long time, and I thought I had a pretty good understanding of that topic. And there was a lot you shared in the presentation in a lot of ways that the endotoxemia impacts the systemic health of the individual that I'd never heard before that I didn't know anything about. It made some things make more sense that when people say, "Oh, I started to do this thing for my health, or I started taking the spores and this happened, or I started this..." All these seemingly unconnected to what the person is doing, benefits largely I think are coming from this situation of a reduced endotoxemia load on the body.

So that's what we're going to talk about today. If there's still anyone in our audience who don't know Kiran, he is the chief science officer and founder at Microbiome Labs and now with Novozymes North America and one of the most prolific teachers I was making the jokes about the travel. If you guys aren't in the loop, Kiran flew 80 bajillion miles a year before COVID started. What was your record?

Guest: Kiran Krishnan:

About 400,000 a year. But I'll reach that this year too.

Host: Michael Roesslein:

How many laps are on the planet is 400,000 miles. Have you ever done that?

Guest: Kiran Krishnan:

I think that's probably close to 18 laps on the earth.

Host: Michael Roesslein:

So you're winning. It's definitely to the moon and back. The moon is about 220,000 miles away.

The moon and back. So he goes to the moon and back-

Guest: Kiran Krishnan:

A year.

Host: Michael Roesslein:

... teaching everybody what you're going to learn here, but generally on the professional circuit. I mean, he's teaching conferences with medical professionals, doctors, things of that nature. We're lucky enough to be able to scoop him up and drag him in here and get him to teach you guys the same stuff that people are honestly paying quite a bit of money to attend a lot of things to learn. Wow, that's impressive. You're back to that distance. I didn't know so many things were back turned on.

Guest: Kiran Krishnan:

Oh, it's crazy, yes.

Host: Michael Roesslein:

All right. Well, plus working partially in Europe. Novozymes who they're partnered with is in Denmark, so I'm sure that that adds a few miles on to the travel. But I will get out of the way and let you get started and give us what we most need to know about the correlation between leaky gut and endotoxemia and what are endotoxins and what do they do and why does it matter?

Guest: Kiran Krishnan:

Yeah, absolutely. Okay. So just to set the stage, this is probably the most important thing I've been trying to teach doctors and other healthcare professionals for the last six years, and I think you'll come to understand why. There's a very specific physiology in the body that we have to pay very close attention to. And you can basically trace back virtually every chronic illness that we suffer from to a dysfunction in this particular physiology.

I think everybody's pretty familiar that the vast majority of chronic illnesses are a result of chronic low-grade inflammation, right? Inflammation is a big driver of chronic conditions. And in fact, if you didn't have inflammation, even if you had certain lifestyle choices, even if you had genetic factors, the likelihood of a disease showing up is pretty low. It's the inflammation that allows diseases to show up. And so when you think about the vast majority of chronic illnesses and you think about drivers for them and risk factors for them, it always comes back to chronic low grade inflammation.

And as it turns out, the most prolific source of chronic low grade inflammation in your body is leaky gut. But what does leaky gut actually mean? Because it's just such a generic term. So that's what I really want to break down for you guys and really help you understand what leaky gut is and then the structure, the physiological structures that are involved in this happening.

And then the role that the microbiome plays in all of this. Why I think that's so important. I go into much more depth teaching this to healthcare professionals, but I think even to somebody who's just an educated consumer. The reason why it's so important for you to know is because it helps you understand what things can actually help you get better and what things are just acutely phasic, meaning that it may make you feel better momentarily, but it's not really going to resolve the root cause problem.

So that's why things like long term elimination diets and endless use of antimicrobials and rifaximin rounds, one after the other, and all of these kinds of things don't actually help the root cause of the problem because we're not addressing this key driver. So let me share a few slides and we can get right into it. You can see my slides, Michael, I take it?

Host: Michael Roesslein:

Yes, I can. I just want to let everybody know I turn the chat on. Zoom leaves it as blocked default now when you start, and I forgot that they changed that. So you can drop in the chat if you want. You can put questions in the Q&A on the bottom. Either one is fine. Things tend to get lost a little in the chat because it moves quick. But I'll do my best to keep track of questions and if we have time at the end of the hour for questions, I'll try to get them asked for you. So back to you.

Guest: Kiran Krishnan:

Cool. Yes, sounds good. Okay. So this structure here is what I call the ground zero of most health disorders. This structure occurs both in the small and large intestine and it occurs similarly in other parts of the body as well like the brain and the lungs and so on. Of course, without an intestinal epithelium, it's a different type of lining cell. But what's really important to note here is how this is structured. There's a couple of really deliberate things in how biology has designed this structure that we have to pay very close attention to because it's very unique in our own physiology.

So when you look at the intestines and you eat something, it goes into this tube that's open at both ends, right? So your mouth is one opening, the anus is the other opening. So even though something is entering into your digestive tract, it doesn't actually mean it's in your body because your digestive tract is a tube that's open on both ends.

So things aren't actually technically inside your body until they make it past the lining of the intestines and they make it into circulation. Okay? So to give you an idea of how that is structured, when you look at the tube of the intestines, my skin here on my palm would be the lining of the intestines, the hole, and the tube part of it is called the lumen, the luminal side, if you will.

So when you eat and swallow something, it's in the lumen, it's not actually in the body until it goes through the layers of the intestines and then into circulation. It goes past the lining of the gut. So up here, this top part here... Can you see my pointer when I point at things?

Host: Michael Roesslein:

Yes.

Guest: Kiran Krishnan:

Okay. So up here is what we would call the luminal side. So this is a tube part. The next layer from the tube is this mucosa layer, and this is called a mucin one layer. It's not a super solid thick layer, it's more like a loose jello-ish layer, but it's much looser than jello. Jello tends to have a more firm structure. This is where the vast majority of microbes in your gut microbiome live. They live in this top mucin one layer.

So things have to go past that layer first. Then here's this other layer called the mucin two layer. This is an inner mucosal layer that's actually thicker and more solid than the top layer, the mucin one layer.

That sits directly on top of the intestinal epithelial cells, which are the gut lining cells. And those cells, the distinct structure there is that it's only a one layer thick. This is the final barrier between something being outside of the body, which is up here in the luminal side and something being truly inside the body, which means it's gone past this barrier and into circulation.

So down here where you see these immune cells depicted, that's called the basal lateral circulation. Things are now in circulation when they come down here. Now ,when things come down here, 80, 85% of everything that comes down here goes to the liver first. So that goes through what we call portal circulation. And then about 15% go into the general circulation.

But the vast majority of things end up going to the liver. First is the liver has to deal with all of the things coming in, whether it's a toxin that it's trying to neutralize and get rid of or it's a metabolite that it's metabolizing for us. So the liver is critically important in all of this here, but the two structures that are extremely unique in our biology that it's just you cannot ignore it because it's so different and so unique is one is this mucin two structure.

And what makes it so unique is that as it is depicted here, there are virtually no microbes in the mucin two layer. Everywhere in your body you have microbes. Places that we used to think were sterile like your brain or your urine, I always heard that when I was in high school for some reason. Oh, urine is sterile. Your eyeballs, your cerebral spinal fluid, all of these internal regions in your body that we assumed there were no microbes because it'd be dangerous to have microbes in these areas because it'd be infectious and so on, all of these regions are full of microbes.

You're hard pressed to find any part of the body that doesn't have microbes, including in your blood. For every milliliter, you've got about a thousand microbial cells in your blood and you've got 5,500 milliliters. So think about the number of microbes you have circulating around in your blood. 15, 20 years ago, if a doctor found microbes in your blood, they would freak out because they think you're going undergoing septicemia or bacteremia, right?

So we now know that microbes are everywhere except this layer here. This mucin two layer is virtually devoid of microbes. And what's so unique about it is that the layer right above it, the mucin layer above it has the largest concentration of microbes in the body. So there's a very deliberate reason why there is this distinct separation where the largest concentration of microbes in the body is sitting on top of one of the only sterile components of the body.

And in a healthy situation, microbes do not penetrate from the mucin one layer into the mucin two layer even though they're fractions of a millimeter apart. So that's so interesting. There's a very deliberate reason for that. And if we ignore this, if we ignore this physiology, we're missing out on a lot of different healing opportunities looking at root cause medicine. So that's really unique physiology number one.

Really unique physiology, number two is this barrier layer. This barrier layer, which is the final barrier from something entering into the body like the skin as a barrier is actually deliberately designed to be a very robust barrier because there's many different cell layers, including the very top cell layers that are all dead cells. And the reason those dead cells are important because they're not reactive to things like live cells would be, they can just act as a physical barrier against things entering through.

And then when you go through, you look at all the squamous layers and all these cells piled up on one another to make a brick wall. So your skin acts like a very strong physical barrier given that the intestinal epithelium has higher surface area than your skin and gets almost more exposure to things than your skin does, and is the final barrier between something entering directly into your bloodstream, and the fact that it's only one cell layer thick is really, really surprising.

As depicted here, these are cells sitting shoulder to shoulder. This is the final barrier between something entering into the body and staying outside of the body. Now, there's of course purpose for this, right? And the purpose is that we do want lots of things to move through this intestinal epithelium, nutrients, for example, right? That nutrients you digest up here and you start absorbing through here, there has to be a way for those nutrients to get through.

And so that's why this barrier is flimsy, but very dynamic, meaning some nutrients go through what we call the transcellular pathway. They can make their way through the cell themselves. There's receptors up here to pick up the nutrients, transport it through the cell and spit it out the other side into circulation. And then there's the paracellular pathway, which is in between the cells.

Now, in between the cells there are these proteins that stitch these cells together, and those are called clodin proteins. This is their tight junction. So these proteins, what they do is they relax when we want the cells to open up so that nutrients can pass through, and then they cinch up tight and close up the cells when we don't want things to pass through. So this very strict control mechanisms involved in all of that.

Now, if something happens to these proteins and they degenerate, then the cells basically stay open all the time. That's part of the physiological impact or changes that occur when you have leaky gut. The other very unique thing about this intestinal epithelium layer is it's unlike our skin. It's a multifunctional layer, so it actually acts like an immune organ and it acts as an endocrine organ, right? Within the intestinal epithelium, every few cells are these intro endocrine cells because they can sense things that are happening up in this top luminal layer, which is where they get messages from, what's what kind of environment the host is in, and they can change the types of hormones that they produce or induce in order to adapt to that environment.

So it's a bonafide endocrine organ. Your intestinal epithelium is not acting just as a barrier, it's acting as an endocrine organ making hormones for you all the time. Then the other component of it is it's a bonafide immune organ as well because every four or five cells is a different type of immune cell.

You have L-cells and M-cells and paneth cells and so on. Think about that differently from your skin, how the outer barriers of the skin don't have any endocrine cells, don't have any immune cells. They're basically just barrier cells acting as a wall. In this case, this is much more dynamic. There's tons of immune cells in the intestinal epithelium and tons of hormone cells in the intestinal epithelium as well among other cells like goblet cells that actually reproduce the mucin layer.

So it's a very dynamic, unique barrier system. And again, all of this is so deliberate. So why are there so many immune cells in this area? Well, this is the most forward facing component of your immune system. Keep in mind, we don't have any outer immune cells. We don't have immune cells on our forehead and our outer skin to understand what the environment is like that we're in to try to protect the host.

Your immune system is one of the only systems that adapts constantly to your environment. If I were to go, I'm flying out to London tomorrow. When I get to London, what I'm exposed to in London for my immune system is going to be different than what I'm exposed to here. My immune system needs to learn what the exposures are there, what antigens I'm breathing in and so on, and then adapt to those antigens. Or I'm going to feel sick when I get there or I might be more susceptible.

I may not have tolerance of the things that are in their environment and I get hypersensitivity reactions and so on. So my immune system has to be able to understand what's out there and adapt to it quickly. The way it does that is that virtually everything you're exposed to somehow ends up in the digestive tract, right? Because the biggest exposure we get is to the things we eat and drink. So food is a huge exposure to what's happening in the environment around you. Drink is a huge exposure as well.

But keep in mind when you breed stuff in, everything goes into your upper respiratory tract. And then you've got things like the mucociliary elevator in your lungs, these tiny hairs that move all these antigens up to your throat. So you swallow them and it ends up in your gut. Your eyes, your ears, your nose, all of that, all of the stuff that goes in there, those orifices all drain into your throat and then you swallow all of that.

So your station tube is in your ears, drain into your throat. Your eyes drain into your throat. So your nose of course is connected and drains into your throat. So virtually everything you get exposed to when you go out into any sort of environment ends up in your gut and that becomes the largest sampling site there is. So what happens when these things enter in, whether it's food or antigens or toxins or viruses of bacteria from a new place, is that it goes into the gut microbiome. It goes into this luminal side, and if you have a healthy gut microbiome and one that's working for you, you will have these microbes translating these messages to your immune system.

And communicating to the immune system whether or not you should have tolerance to this thing that you're now exposed to or if it's a problem and you need to elicit an immune response. That's something called crosstalk between the microbiome and the immune cells, and the immune cells that they're talking to are the immune cells in the intestinal epithelium, the L-cells, the M-cells, the paneth cells, all of these cells that are found within the intestinal epithelium.

Now, they speak the conduit between which the microbiome and the immune system speak is this mucin two layer. And this is why the mucin two layer is sterile. There's been an agreement to the course of evolution between the immune cells here and all of the trillions of microbes that live up here that, "Hey, we're cool. We know how to work together, but we have to keep a certain distance from one another."

So this proximity to the immune cells in here is extremely important, meaning we need these microbes to be close but not too close. So that's one of the key roles that the mucin two layer plays is it provides a proximity comfort for the immune cells in the intestinal epithelium that allows those immune cells to not overreact and yet communicate with the microbes that are up in mucin one layer.

If this proximity is encroached upon, meaning if this layer gets eaten up or broken down somehow and all of the microbes in the mucin one layer move closer to the intestinal epithelium it starts to freak out the intestinal epithelium cells causing them to elicit really robust immune responses at the lining of the gut.

So this is what I call the de-militarized zone. If this zone exists, then the immune system and the microbes can talk happily. The immune system can adapt, the microbes can communicate what it needs from the immune system because the microbes do that, right? So for example, when you're eating food and food is passing through your small intestine. You release bile in order to help not only detox from any fat soluble toxins that are in the food, but also to break down and absorb fatty acids and fat soluble nutrients.

And then as the bile is circulating through, when it goes back into the liver at the very end of your small intestine, it triggers a receptor called a nuclear FX receptor, which then causes your intestinal epithelium immune cells to release antimicrobials into the mucin one layer to bring down or reduce the growth of microbes. That's one of the ways in which our body protects us naturally from SIBO from overgrowing bacteria in this small intestine. And the microbes in the small intestine love that because they don't want a whole bunch of non-native microbes coming in there and overgrowing which was what happens in SIBO.

You get all of these gram-negative non-native bacteria to that region overgrowing. So the local bacteria, the gram-positive indigenous bacteria to that region are very happy to trigger the intestinal epithelium immune cells to release antimicrobials to maintain the low levels of microbes.

That's just one example in which the intestinal epithelial cells produce things that are useful for the microbes in maintaining the ecosystem there. So there's this constant crosstalk. All of that gets dismantled the moment you start losing this demilitarized zone. So the vast majority of diseases will occur because we have somehow compromised this mucin two layer.

Think about even just really deadly conditions like colorectal cancer. 50,000 people this year will die from colorectal cancer. We know celebrities that have been diagnosed and don't make it very long, despite looking and seeming quite healthy and so on. Colorectal cancer starts because two microbes move from this mucin one layer slightly into the mucin two layer.

Bacteroides fragilis and E coli. Those two microbes move from this layer into this layer, just a millimeter or two move. They start setting up shop producing inflammatory compounds, starting the inflammatory damage that occurs to the intestinal epithelium. And in some people, that inflammatory damage will lead to the formation of tumor cells. Now, you have colorectal cancer.

So 50,000 people will die from a devastating condition because two bacteria went from here to here. That's how important the structure is. If we're not maintaining homeostasis and regenerating the structure in those who have it broken down, it becomes really hard to heal from anything.

So what within the microbiome maintains this structure? Number one, high diversity, high levels of alpha diversity. That means more viable species in the gut microbiota will maintain this structure for us. And then the presence of critical protective strains. These are called keystone species like akkermansia, like faecalibacterium prausnitzii, like bifidobacterium longum, all of these organisms have been shown to be inversely correlated with disease.

Akkermansia, for example, is inversely correlated with everything under the metabolic syndrome spectrum. That's like 40 plus conditions. If you have high akkermansia, you're protected against all of those conditions. How does akkermansia protect against all those? And we're talking about obesity, diabetes, cardiovascular disease, polycystic ovarian syndrome, dementia, all of these conditions. How does one bacteria protect against all of that? Does it have a magic compound that it produces for each of those conditions? No.

The way it protects against those conditions is because it plays a very critical role in maintaining this mucosal structure. So just from doing that, this bacteria can protect against almost 60 different chronic conditions. And the studies in akkermansia are absolutely clear. When you have high akkermansia, you have very low risk for all of these conditions.

Faecalibacterium prausnitzii is another important one to note. Faecalibacterium prausnitzii is inversely correlated with everything under the inflammatory bowel spectrum. So Crohn's, colitis, micro-colitis, colorectal cancer, and so on. All of those conditions, devastating conditions are protected against if you have high faecalibacterium prausnitzii.

So how does it do it? Does it produce some special compound against those disease? Nope. Faecalibacterium is very well known to regenerating and maintaining this structure. So that's all it does. One of the key things of how these microbes protect against the destruction of this structure is the production of short chain fatty acid. So butyrate propionate and acetate. Butyrate propionate and acetate Are very critical in maintaining the structure. Butyrate, for example, is a primary fuel for the intestinal epithelium cells. So to get them to repair and turn over when they're damaged, you need more butyrate so that you don't leave giant gaps in the intestinal epithelium.

Goblet cells that are responsible for making this mucin two and mucin one layer because you have to keep regenerating this layer. Goblet cells require butyrate in order to make the mucin one and mucin two layer. And then finally well formed type junctions. We need those proteins in between those cells to be stitched up right, be able to relax when something has to get through, but cinch up when something should not get through.

So the presence and the expression of the tight junction proteins so far we know only come from signals from the microbiome, especially from a highly diverse microbiome. So if you don't have the right microbes, you're not getting the signals to express those proteins. And anytime they get damaged, the cells remain apart and your gut remains leaky the whole time.

So that is important to note. Let's talk about a couple of the drivers that drive this, and this is what it starts to look like when your gut is leaky. You lose this mucin two layer, which means that the microbes and all of the things up here are stuck in the mucin one layer translocate to the inner part where the intestinal epithelium is. As all of these microbes start moving closer to the intestinal epithelium, you're breaking that proximity comfort zone, and that means all of the immune cells in the intestinal epithelium start recruiting all of these inflammatory immune actors like natural killer cells and dendritic cells and macrophages and you start getting a massive amount of inflammatory response right at the lining of the gut.

What that ends up doing is it ends up damaging your gut lining cells, leaving big gaps and holes and allowing for things like lipopolysaccharide, LPS to leak through and enter into circulation. Remember when it goes in here, 85% of it goes to the liver. The other 15% or so goes directly into circulation. So the part that's going into the liver is driving massive amounts of toxicity and inflammation to the liver because it's a very powerful toxin made in your gut microbiome. So it's an endotoxin. It's not one that you can get away from compared to an exotoxin which is something from the outside that you can get away from if you have to.

But this endotoxin that is produced by about 50% or more of the microbes in your gut, that endotoxin is constantly leaking through if your gut looks like this. And as it leaks through, not only is it going to the liver and then creating inflammation in the liver, but the 15% that circulates around directly causes massive amounts of chronic low grade inflammation throughout the body.

So it becomes one of the most prolific drivers of chronic low-grade inflammation. Now, this LPS can do lots of other things as well. For example, when it gets into the brain, it can actually bind and interfere with serotonin receptors and dopamine receptors. So it interferes with your body's ability to bind and utilize serotonin and dopamine.

It also shifts tryptophan metabolism. So all the tryptophan you're getting from your diet is not being produced into melatonin and serotonin, it's being produced into kynurenine and quinolinic acid, which creates massive amounts of neuroinflammation and of course negates sleep, negates happiness makes you much more susceptible to anxiety, depression, and so on.

The LPS also has been shown when you have elevated levels of LPS in circulation. It's been shown that it dramatically increases the risk for autoimmune disease because LPS in circulation can act as an environmental trigger to trigger autoimmune disease. We also know that when LPS interacts with fat cells, for example, in your midsection, when it leaks through, it swells the fat cells almost three times its size.

So you can get this really kind of swell, bloated feeling and actually start increasing the volume of your fat cells. And thus, LPS is a key component to putting on weight as well. So in screws with almost everything in the body, as I mentioned, the presence of this LPS endotoxin in the blood leaking through

this dysfunctional barrier is called endotoxemia, right? And if you have LPS elevated in your circulation that is absolutely the root cause of any chronic condition that you're feeling, right?

So here's what drives this whole process, dysbiosis. That's a generic term that just means imbalance of microbes in your gut. But how do we actually measure and think about dysbiosis? Number one, it's a loss of keystone species. These are, remember, the organisms that rebuild this mucosal layer constantly. And these are akkermansia. Faecalibacterium, I mentioned them before. Having low diversity levels because if you have low diversity, you don't have enough microbes to speak with the immune system to sample things that are coming in from the environment and to also resist the overgrowth of certain pathogenic and problematic organisms.

So diversity is critically important as well. Then you start losing the production of things like short chain fatty acids. You get this disrupted mucosal system, disrupted mucosal immune response. And also, here's a really important note, the gut mucosa. This mucin two layer especially is like the central command center for all of the mucosal tissue in your body, your lungs, your brain, your eyes, your urogenital tract, and so on. So whatever's happening in the gut mucosa gets translated to all of the MCO mucosal tissues.

So your gut mucosa is heavily inflamed because you're dysbiotic, there are too many microbes eating away at that mucin two layer, and you get this inflammatory response in your gut in the mucosa, that's the same kind of response that's going to get translated to the rest of the mucosal tissues in the body. That's why if you have a disrupted gut, you're more susceptible to asthma in the lungs or sinus problems or UTIs and BV and so on, because all the mucosal systems immune responses are compromised because your gut mucosa, the central command center is not functioning properly.

Again, everything ends up with this barrier system being dismantle and then LPS leaking through and making it all throughout the body, including in the brain. So LPS goes directly into the brain pretty easily.

Now, dysbiosis is merely described as an imbalance of microbes that eat away at the mucin two layer versus microbes that rebuild it. That is the fundamental difference and the fundamental driver of dysbiosis. If you can up the microbes that rebuild it, even if you have microbes that eat away at the mucin two layer, that's still fine. You'll be in a healthy state.

But if you have too many microbes that eat away at the mucin two layer and not enough to rebuild it, you will end up with a chronic illness. Because that's chronic low-grade inflammation all day long. I just want to show you this electron micrograph that's so fascinating. This is exactly what we depicted in that animation. Up here is a mucin one layer with all of these microbes up here. You see just high density trillions upon trillions of microbes when you look at the entire digestive tract.

Here's in green, the mucin two layer. No microbes in there at all, with the exception of this one blip here. I don't know if this is a blip in the rendering of this or one microbe did make his her way down here. But for the most part, keep in mind that this is a very sterile environment given, especially that it's sitting right below the most dense area of microbial diversity.

And then these blue cells share the intestinal epithelial cells. So this is a cross section look, and I think it's a micrograph look of that lining. So this is why we have to pay attention to it. This is a very deliberate and unique structure in the body. This is the only structure in the body that is sterile. Nowhere else in your body are you sterile, and it's just crazy that it's sitting right above the highest density layer of microbes anywhere in the body.

This is probably 2,000 square feet or so in your gut. So the only sterile component in your body is one of the largest surface areas, which is also in your digestive tract. Now, once LPS leaks through, it's very pervasive. It gets into virtually every corner of the body. Everywhere it goes, it elicits a massive inflammatory response. So if you constantly have LPS leaking through, through a dysfunctional barrier, a

dysfunctional microbiome, and then tight functions all that are opened up, if you have LPS continuously leaking through, you will have chronic low grade inflammation. And if you have chronic low grade inflammation, that becomes a root cause of the vast majority of disease conditions. And it continues to drive those conditions, even if you're trying to treat that condition in a different way.

If you still have the leakiness in the gut, if you still have this barrier dysfunction, you will continue to progress in that condition. So it becomes really important. This is why I travel so much because I'm trying to press upon healthcare practitioners that they have to pay attention to this layer and that all of the therapeutics approaches that they take have to have something in it that addresses the rebuilding of this layer.

So that is the super important part. There's lots and lots of studies here that I tend to show how LPS, endotoxemia drives all of these disease conditions. I'm not going to go through this with you guys, but just know that there's tons of papers that show how endotoxemia initiates all of these conditions in the case of obesity and insulin resistance.

If somebody is endotoxic meaning their gut is leaky and dysfunctional, every time they eat, they get a massive amount of endotoxins. In circulation, those individuals were severely endotoxin to begin with, but maybe of normal body weight. But then as the endotoxin gets worse over time, then it'll start to actually initiate the formation of adipose tissue making people overweight.

Let me go to... And this is so many things. Type two diabetes. The number one driver, and the best predictor of going from being pre-diabetic to type two diabetic is the presence of LPS in circulation. We know LPS also drives anxiety depression. We know that LPS also creates brain degenerative conditions like Alzheimer's, Parkinson's as well. We know that cancer having leakiness in the gut and having elevated LPS levels is a big driver of Cachexia or wasting syndrome and cancer, which is the biggest driver of mortality in cancer.

It also impacts fertility. So if there's an elevated amount of LPS in circulation, in utero, it can actually disrupt the formation of the female sex organs in utero itself. So neonate getting exposed to LPS in mom's body can have a transgenerational female reproductive impact because the LPS can already start to create dysfunction in the urogenital tract of that baby.

So it plays so many roles. It's actually the biggest driver of low testosterone in men. SIBO to me, endotoxemia is the biggest driver of SIBO. We could talk about this in the Q&A sessions that people want to know. Other problems like acute diseases, autoimmunity, everything, COVID. Even we know that COVID has a capability of binding to LPS to enter into cells.

And then of course, if you have any of these chronic conditions, it's likely because you're highly endotoxic. And when you're highly endotoxic, you have really high levels of basal inflammation. Those are the people that really succumb to COVID for the most part. So that was an underlying risk factor.

All of these conditions, leptin resistance, chronic constipation, cognitive decline, memory recall issue. Let me just go here so we can talk about what we do as a solution. So maybe I'll stop there. Michael, I know I've been rattling a lot of information out and maybe tackle some questions that are there and then I could talk about what we do to deal with the endotoxemia.

Host: Michael Roesslein:

Yeah. Great. Thank you. I'll try to keep it to leaky gut and endotoxemia related questions. Test for leaky gut. Somebody says, "How do we know if someone has leaky gut, especially in small intestines?" I know in your published study that you did with MegaSpore, it was you were measuring blood levels of LPS post prandial, so after meals. The spike of LPS was one way of these lipopolysaccharides, these endotoxins to measure the amount of permeability. Because if there's no permeability, there's no LPS.

So that's one way. I know there's a lot of different kinds of tests. Do you have any feedback other than that on that question?

Guest: Kiran Krishnan:

Yeah. So the kind of test that we use in the research lab isn't commercially available. There's just some cumbersome aspects to it that don't render it to being useful in the commercial setting. There isn't a direct test on LPS in the consumer space. There are a couple companies that do an antibody test against LPS, companies like Vibrant and Cyrex. The only problem with the antibody test is it's a secondary measure because it's also dependent on how effectively your body produces antibodies and what kind of antibodies.

So basically what those tests are looking for are antibodies against LPS in circulation. But again, we're depending on your immune system to respond properly to LPS, produce enough antibodies before we can even measure it. So they're not the greatest approaches. But here's what I'd say about endotoxemia and leaky gut. In our studies in healthy young individuals, these are people with normal body weight, no chronic illnesses, not on any medication for anything, perfectly fine in the peak of their lives. 55% of them had very severe endotoxemia, meaning very high levels of chronic inflammation that are due to leakiness in the gut.

If it's 55% of that population, if you think about a population that's had any symptoms at all, whether digestive or immune or hormonal or whatever it may be, it's likely 98 to 100%. So I think you can assume you have leaky gut if you've had any sort of metabolic inflammatory type of conditions, and then address the leakiness of the gut.

Host: Michael Roesslein:

Great. Let's see. We'll talk about increasing microbe diversity in a minute. Zonulin was something that I heard a lot, mentioned a lot when I was going through training with FDN and learning to read lab tests and things like that as a marker for leaky gut. You didn't mention that just now.

Guest: Kiran Krishnan:

Yeah.

Host: Michael Roesslein:

There's just a general question about Zonulin and being a part of a leaky gut and what to do about it.

Guest: Kiran Krishnan:

Yeah, so Zonulin is a direct measure, but the problem with it is it's not always associated with leaky gut. And you don't have to have leaky gut if you have elevated levels of Zonulin. Because again, you're typically measuring it, whether it's a stool based test. I think the most common way to do it. It's about, I would guess about 50-50 where it's telling you about the leakiness in the gut. But the problem to me is it doesn't tell you why your gut is leaky like what aspect of it is off.

So I genuinely think there's no need for us to diagnose leaky gut. It's easy to assume that you have leaky gut, right? No different than if I haven't had water in two days. I don't need to measure my level of hydration to know I'm dehydrated. There's lots of symptoms of dehydration. So I just drink water until those symptoms go away. And the same thing with leaky gut. The world we live in today, the low load diversity that our gut microbiome tends to have, the antibiotics we've all taken, all the things we get exposed to. And then when you look at all the conditions that are supremely present that are leaky gut

associated, you don't need to test and diagnose a leakiness in the gut to know that you should address it.

Host: Michael Roesslein:

Gotcha. Can LPS be measured? Yes. Can one see changes in LPS when intervention? Yes. That's the study they did. That's a blood marker. That's not a common marker on lab tests. I don't even know if functional practitioners have access to ordering that or if that's like a clinical trial thing. Do you know?

Guest: Kiran Krishnan:

It's a clinical trial thing. Yeah. The problem is it is a blood sample and then you have to separate the serum, right? The problem is LPS, when you pull it out of the body has a relatively short half-life like four hours, which means that what you either have to do is be able to test it in the HBLC which is a kind of liquid chromatography testing. You have to be able to do that within the first four hours, which doesn't happen because when a doctor pulls samples, they're going to be shipping the samples to the lab.

It may get tested within 24 hours, but definitely not four hours. Or you have to freeze the samples at minus 80 in order to keep the LPS stable. So what we do at the university as patients are coming in and so on, we freeze all of the samples that we extract and then run them all at the same time. Commercially, you just can't do that.

Host: Michael Roesslein:

Gotcha. For our shelf life would make that a pretty difficult in a commercial lab. Can you assume you have leaky gut if you have SIBO?

Guest: Kiran Krishnan:

A hundred percent. Yeah, you absolutely have leaky gut. And it's the leaky gut that's likely the original source of your SIBO too, which means that you probably cannot improve your SIBO without addressing leaky gut.

Host: Michael Roesslein:

All right. Which blood markers for inflammation are most likely elevated by... When you say blood markers for inflammation are elevated by increased LPS or endotoxemia, they asked C-reactive protein, homocysteine LDH, something else. Are you looking at individual cytokines? What's the markers?

Guest: Kiran Krishnan:

Yeah, let me see. I think I have them here. These are the main ones. It's MCP1, which is a chemokine that indicates recruitment of immune cells to the lining of the gut, which is what's happening when your gut is leaky and you've eaten away at that mucin two layer. You're getting this translocation of all the microbes, so those immune cells in the intestinal epithelium are constantly recruiting innate actors for that area.

Interleukin 12P, interleukin 1 beta, interleukin 6, and interleukin 8. You can also use something that they've done in a lot of HIV studies because leaky gut in this kind of leaky gut, this endotoxemia is the most prevalent driver of mortality in HIV. Right? And this is published by the NIH. So there's been a number of studies on HIV and leaky gut, and they use a surrogate marker called soluble CV14. So it's called SCV14. And I think most of the main labs can do that, but it's a surrogate marker. So it's not a direct measure. It'll give you some idea, but it's not a direct measure on to your LPS levels.

Host: Michael Roesslein:

Okay. That makes sense. All right. Guys, please keep the questions in the Q&A. I've got to close the chat to stay up on the Q&A. So if your question is in the Q&A, I'll get it, but they'll get lost in the chat. "Will LPS show up on live blood analysis?" I have no idea. I don't know anything about live blood analysis.

Guest: Kiran Krishnan:

I don't either. I'm not familiar with that.

Host: Michael Roesslein:

Okay.

Guest: Kiran Krishnan:

I would guess not.

Host: Michael Roesslein:

Skin issues linked to leaky gut. Yes, that's actually one of the most prevalent symptoms, I'm guessing, related to the flooding of the liver because you said everything that comes through the gut lining goes in the liver, overloads on the liver tend to end up on the skin. Jen Fugo, I believe is going to be presenting on that kind of trifecta for our new toxicity masterclass coming up in February.

All right. What was the study that shows HIV is... I know it's driven by LPS, but is severity of disease related to endotoxemia levels? You mentioned that I believe. Do you have it in any of the slides?

Guest: Kiran Krishnan:

I don't think I have that on these slides, no.

Host: Michael Roesslein:

Okay.

Guest: Kiran Krishnan:

Basically it was a study that indicated that the best predictor for mortality in HIV and AIDS was the degree of endotoxemia that the individuals had. It was a better predictor than viral load itself. And then there's also studies that show that the key determining factor of progression from HIV positive to actually having AIDS, the acquired immunodeficiency syndrome is the amount of LPS and circulation. So the more inflammation you have, the higher amount of chronic low grade inflammation you have, the higher the susceptibility is to going from HIV positive to AIDS. So there's been both of those kind of studies.

Host: Michael Roesslein:

Okay, great. [inaudible 00:50:42] Okay. Regarding the traditional lab markers of inflammation, the things C-reactive protein and such, there's a ton of factors that impact those. So yes, I would guess addressing something like this and having lower LPS and lower gut related systemic inflammation would be helpful. And there's a lot of other things that drive stress levels increase C reactive protein and homocysteine, so there's just a lot of different factors that play a role there, but yes. All right. Okay. So most of the questions are... I'll try to get to a couple more. How many minutes do you have?

Guest: Kiran Krishnan:

I think about five, six more minutes.

Host: Michael Roesslein:

Okay. I've got way more than we can do. They're getting posted in there faster than I'm able to ask them, so they're going like they're multiplying faster than we're reducing them. So what I'm going to do right now is I'm going to copy the Q&A into another document that I will have, and then I will read through that and I might send you an email with a couple questions in it.

Guest: Kiran Krishnan:

Okay.

Host: Michael Roesslein:

We did a whole bunch of questions. Sorry, folks. We got to stay within the time thing. I've got them all that are in the Q&A right now and I will see what I can to get some of them answered for you. Before you get into these three, I know you guys developed this specifically for this problem and tested it and everything, and the lab tests or the studies are pretty incredible.

Before supplementation, just a few quick switches or fixes or changes or flips to either diet or regular lifestyle or anything that you can recommend to that somebody could implement tomorrow. And then you can share with us what you guys have created to address this situation.

Guest: Kiran Krishnan:

I think people should be doing non-supplement things as well. So I think it requires a comprehensive and active approach in maintaining that barrier system in the gut and not allowing it to become leaky. So some of the non-supplement things that you should be doing is working on increasing the diversity of your diet. So adding in more roots and tubers and plant-based foods.

The more restrictive your diet is, the lower diversity you tend to have within your gut microbiome. So start trying to add back certain foods, one a week, something like that, so that you can increase the diversity of your diet over time. Intermittent fasting can certainly help as well. There are lots of organisms that grow better when you're not eating food. And so giving your body rest for some time.

I intermittent fast almost every day, but most of it is overnight. So whatever time I stop eating dinner at 8:00, 9:00 let's say, then I take a 14 to 16-hour break. From that point, six seven hours, which is overnight and then another four or five hours in the morning before I have my first caloric meal.

So that is an important thing you can do as well. Reducing the use of chlorine and Clorox based compounds cleaners in your home. You don't have to sterilize every environment in your home. Maybe your toilet you want to do it or your shower, that's fine, but vast majority of surfaces in the home shouldn't be sterile. And you want to develop a bit of a home buyer so that you've got a healthy microbiome within the home, which will support your own microbiome.

Staying away from non-organic food and things that have high levels of glyphosate or Roundup, that can be quite helpful as well because those things act as really strong antimicrobials and create dysbiosis in the gut. And another simple one, and it's a wonderful option, is getting a dog. So dogs really increase the diversity of the microbiome of the household and overall your gut and your immune system will do better if you have a dog, assuming you're not severely allergic to dogs.

So those are some of the simple free things. Oh, one last thing is mindfulness work. So if you can control your stress response to some degree through mindfulness work programming, reframing things, that can be really, really powerful because stress will induce dysbiosis, right? Stress shifts the balance between microbes that eat away at the mucin two layer versus microbes that rebuild it.

And because it does that, it can drive leakiness in the gut very significantly. And then it puts you back in this cycle of having that leakiness in the gut and then that leakiness causing more stress and then that additional stress causes more leakiness and so on. The cycle keeps repeating.

Host: Michael Roesslein:

Right. Perfect. You're great. Did you want to get into a little bit of the slide here?

Guest: Kiran Krishnan:

Yeah. So let's talk a little bit about the supplementation options. So we develop MegaSporeBiotic, which is our foundational product, the flagship probiotic specifically to address leakiness in the gut and endotoxemia. So we've published a couple papers that have already shown this. We've got a bigger study going on right now that just finished. So we'll have three, four different studies to show that MegaSpore stops endotoxemia in a very significant way.

Now, on top of that, it starts increasing the diversity of your microbiome because it lifts up organisms that are at very, very low levels. And then it also competes against pathogenic organisms that seem to be fighting against good commensal bacteria and causing a disruption in the gut ecosystem. So those are just some of the things that the spores do. The spores also do increase the expression of tight junction proteins. We also know that the spores have a modulatory effect on the immune system in the gut and systemically as well, so they can reduce some of that really unfavorable inflammatory immune responses that are going on in the gut.

So we always start with reconditioning the gut using the bacillus endospores. After taking that for about 30 days, your gut is already starting to get on the right road. We want to reinforce those changes by using the right type of prebiotic. So that's why we have this MegaPre, which is a selection of oligosaccharides. And the reason why we pick oligosaccharides is because they're your first foods from your microbiome. Because mother's milk contains upwards of 200 different oligosaccharides.

Also, what we've been able to show in a published study is that these oligosaccharides enhance what the spores are doing. The spores are increasing diversity, increasing keystone species, reducing problematical pathogenic organisms. What we find is that when you add the MegaPre to it almost triples all of those factors. So if it was increasing short chain fatty acids like butyrate production by 50%, when you add in the prebiotic, it's going to go up to 150%.

That's the actual data that we have in the published study. So you start to recondition your gut making changes so that population and so on. And then you bring in the MegaPre to reinforce these changes. So then you're consuming both the MegaSpore and MegaPre in month two. And then the final stage is rebuilding the gut mucosa. We use a product called MegaMucosa which has IgG, which is really important for reducing inflammatory damage in the gut.

We have polyphenols. Polyphenols also reduce inflammation in the gut, but then they also feed akkermansia. That's one of akkermansia's favorite foods. So these polyphenols can play a really important role in dampening that inflammation and dampening that continuous irritation that creates damage.

Most importantly, we have four key amino acids in the product. And the reason why that's so important is because studies have shown that when you have those four amino acids, it increases the rebuilding of

the mucosal layer by 95%. So all of these products are designed to, in normal cases, this is your first 30 days where you do just doing MegaSpore. The second 30 days, you're doing the MegaPre and with the MegaSpore, and then the last 30 days you're doing all three of them. MegaPre, MegaSpore and MegaMucosa, all of them together.

So this whole system is designed to revamp and change what the gut microbiome looks like especially with respect to that structure, the intestinal epithelium structure. And if you don't do that, it becomes really hard to make progress in chronic illnesses because that endotoxemia process is one of the number one drivers of chronic illness.

Host: Michael Roesslein:

All right. I know you got to run. The studies we have, 13 of them listed on one of the recent webinars we did. You went through the studies. I'll make sure to send out links to the most relevant stuff on our site when we send out the recording to this webinar, because we have those studies in one place. We have a whole post on this TGR trio and how to best utilize it and everything. So I'll make sure to include that in the email that goes out with the recording to this. I copied over 26 questions from the chat. I will try to summarize things and send you a handful of questions possibly if you can respond at an email.

I will do a followup to get as many answers as I can to people. And as always, thank you. Like I mentioned at the beginning, this invitation stemmed from the presentation he gave which was all those slides that were skipped over here plus some other stuff. It got really in depth and it was really in detail. So there's a presentation coming soon that will air in February that will be part of our Toxicity in Detoxification masterclass that takes a much, much deeper dive into this. I just really wanted to get the information out there quickly. So thank you, Kiran, for jumping on to do this. I know it's in the middle of your day there, so I appreciate it. And you can hop off and I'll chat with them for a minute and let's connect again soon.

Guest: Kiran Krishnan:

Awesome. Thanks, Michael. Thank you, everybody. Thanks for hanging on. We'll see you again soon.

Host: Michael Roesslein:

All right. So thanks, everyone. I know that was kind of fast there. I wanted him to just load as much information as he could into the hour that he had. I will send out a recording as soon as we get it set up. We also put all the Microbiome Lab stuff on sale for this weekend. I put it in the chat there. It's 10 bucks off any two Microbiome Labs products. So there's a coupon there. There's a link there that goes to the shop for Microbiome Labs in our shop. But I did copy over a ton of questions. I will try to get them all summarized and sent over to Kiran and we'll try to get as many answers as I can.

Some of them I know answers to because I've done a ton of these webinars with Kiran, so I know the answers to a lot of the questions because I've heard him answer them. But we usually like to try to get through all the questions, but today was kind of... We had one flat hour and I wanted him to spend as much time as possible teaching. So you will get a recording. You will get a transcript. So we will have the transcript for this, for those who prefer to read. We're aiming for some time this weekend.

So as always, you guys brought great questions. I will do my best to answer as many of the questions as possible. Maybe I'll do a post or an email just solely on the questions after we do the recording and everything else because it might take a few days to get ahold of Kiran. I apologize if I'm a little slow. I'm on the back end of two and a half weeks of nonstop travel and it is nighttime here.

Thank you everyone for hanging out. We had 150 people on live in the middle of the day on a whatever day this is, Thursday. So thanks for bringing the awesome questions. I've got a ton of them copied over. We'll do my best to get them answered. Darcy, your question about the BiomeFx test, it's usually about four to six weeks for the results to come in, so I saw your thing in the Q&A. If you sent it at the end of October, you probably got about three or four weeks left before we get the results. And then someone from our team creates a results video for you. But you're welcome to email. Somebody will fill you in on that as well.

So thanks, Sarah, Chris, Vera, Michelle, Darcy. Thank you, everyone. We'll be back soon with more fun stuff to learn. See you everybody later.