Introduction to the microbiome and immune surveillance

But then the big question is, how in the world does the immune system survey this huge surface area that's already covered in microbes? How does it survey it for microbes, right?

If we're already full of bacteria and viruses. Yeah, what's good, what's bad. Exactly, what's good, what's bad. How does it actually do that? And when you look at the numbers, there's a 200,000 to one ratio for every one immune cell that you have that surveys the system, you have 200,000 microbes in that same area, right?

So it's a mind boggling task for the immune system to survey that entire surface area. The only way the immune system does it is through crosstalk with the rest of the microbiome.

So the microbiome that exists in your mucosa acts as the neighborhood watch for the immune system. is Doctor Talks, real talk from real doctors on the issues that matter to you most.

Hi, it's Dr. Kent Holthorpe with another episode. Today we have Kiran Krishnan. Today he's going to talk about unhealthy gut equals unhealthy brain. So thank you so much for being on and taking the time.

I know we use your product. I know it's number one seller to doctors and well research, which of course we love. Kiran is a research microbiologist, has been involved in the dietary supplement nutrition market for the past 20 years.

He comes from a strict research background has spent several years with hands on our indeed the field of molecular medicine and microbiology University of Iowa.

He left the university research to take several leadership positions and global companies and business development and product development. Most recently, he's co-founder and chief scientific officer at Microbiome Labs, a leader in the microbiome and probiotic research.

He's a frequent lecturer. We see him at all the conferences on the microbiome, epigenetics, and basically all the main conferences. We see him and he's a lecturer and a great teacher.

He's an expert guest on national radio and satellite radio and has been a guest speaker on several health summits as a microbiome expert, seen him all over the place.

He's currently involved in over 18 novel human clinical trials. I'd love to hear about that on probiotics and the human microbiome. He's also on the scientific advisory board at seven other companies in the industry.

So well respected. And he has published clinical trials, peer reviewed scientific journals. and has several global patents, which I did not know. So thank you for being on.

And it just, I think, really fits with peptides, with epigenetics, and they really dovetail together. We talk about the gut-brain axis and so much research on the epigenetics of the gut.

What the microbiome is and why it matters

And you're right there on the cutting edge. So I can't wait to learn what's new and for all our listeners. And just to go through the basics, what is the microbiome?

Because people hear it all the time, microbiome, microbiome. What does that really mean? Yeah. And Ken, thank you so much for having me. It's such a pleasure to be here.

It's always a great opportunity to be able to nerd out with somebody on this stuff. So I really appreciate the opportunity. So yeah, that is a really important question.

What is the microbiome? And especially, what aspects of it are the most important to pay attention to as we look at health, wellness, and our outcomes?

The microbiome is defined by the scientific literature as really the collection of organisms and all of their genetic elements in relation to the host and of course we are the host.

The second part of it is actually even more critically important than the first part. The second part being all of the genetic elements, right, because that's really where the rubber hits the road.

What are the genes within the microbiome coding for? You know what are the activities and small molecules and metabolites and so on that they code for, because as it turns out, we are really inadequate in terms of function as a human species right if you look at a human chromosome.

We've got somewhere between 22,000 to 24,000 functional genes. And for those that don't know genetics, it sounds like a lot. But when you look at an earthworm or a rice plant, they have somewhere around 38,000 to 40,000 functional genes.

So we are half as sophisticated as an earthworm is. from our genetic perspective. So then the big question was, how is it that we do all of these amazing high order functions that we do?

During the human genome project, when they first mapped out the entire human genome, the estimate prior to mapping out the entire human genome was that we would have somewhere around 150 to 200,000 functional genes, just considering all of the biochemistry that happens in our body, right?

But as it turns out, we have a minuscule number of genes compared to the functions that we have. And that left a big, huge question as to how do we do the things we do?

Then when the Human Microbiome Project came about and we started to realize that, wow, we've got 22,000 to 24,000 human genes, we've got over three and a half million microbial genes in our system.

So so much of the activity, 90 plus percent of all of the metabolic biochemical genetic activity that occurs in us comes from the microbes. And so what does that gene pool look like?

It's mind-boggling. When you think about it, when you look at evolution, one of the interesting aspects of the lineage of mammals One of the things that made mammals much more sophisticated in general over non mammalian species was the incorporation of a large fermentive base.

in our digestive tract. Because what that allowed us to do is it allowed us, number one, to utilize energetics and energy from a larger breadth of molecules, things like plants and seeds and nuts and all of these things that we can actually ferment and digest versus take an obligate carnivore like a lion.

If the lion's food source is gone, the lion can't just go eat plants and fruits and survive. The lion's going to die. we are these amazing omnivores because of this large fermentive base.

Then also, we create the symbiotic relationship where this large fermentive base provides us all of these unique chemical capabilities and biochemical capabilities that we've now counted on for our function because we can't do these things for ourselves.

So we cannot overstate the importance of the microbiome when it comes to health and wellness. That's interesting. So it saves us an efficiency where we don't have to make it.

But then if we don't have the right microbes that we've been counting on for millions of years, we're in trouble,

which seems like where we are right now, right?

Absolutely. And in fact, if you look at some of the top microbiome researchers, one of the themes that we are dealing with that is scary, especially from someone like me from a microbiology perspective, is we're facing a mass extinction right now.

And I'm not talking about animals that are out there in the ecosystem. I'm talking about our own ecosystem inside. what we're seeing based on studies on, you know, hunter gatherer tribes like the Hadza tribes and the tribes in Papua New Guinea that live an ancestral life, similar to what humans did for 99.99% of human existence, that they have almost double the number of microbial species in their microbiome than we do.

And every generation, it seems to be decreasing by a certain amount. And every time we lose certain groups of microbes, we lose huge amounts of functionality.

Because again, 90% plus of all of our biochemical metabolic processes are coded for by bacteria in our system. So what is that going to look like a few generations from now when our kids' kids have half the microbial diversity that even we have, right?

What are they going to be missing from a functionality standpoint? And what is that going to lead to when it comes to disease? Wow. And so I can imagine they probably never had heart disease and they're getting heart disease earlier and all these other diseases of aging and death.

Absolutely. Well, and many estimates are that this next generation, our current generation of kids are going to be the sickest humans in the history of mankind.

It's absolutely mind boggling. If you look at the CDC data, even from just a few years ago, six out of 10 American adults have at least one chronic illness, right?

And four out of 10 American adults have multiple chronic illnesses. 40% of the adult population is dealing with chronic illness. That's scary. Everyone's sick.

And younger and younger, you know, you're at a cocktail party, what's coming up and I'm sick or my sister's sick or something.

Microbial loss, chronic disease, and early-life development

And I'm thinking, I don't think I saw that 20 years ago. All right. So you're diving deep into peptides and longevity on this podcast. And we're right there with you.

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It's time to elevate your journey, starting now. No, no. And you look at the incidence rate of allergies and asthma in kids, of course, you look at things like autism spectrum, and then anxiety and depression.

Oh my God, you know, both in the pediatric side and in the adult side, it's an absolute epidemic. right, of cognitive dysfunction. And this microbiome starts in utero, correct?

That's right. Yeah. So, you know, the kid's microbiome, the infant or the child's microbiome in utero is already starting to develop. There's some evidence that mom's immune cells will actually grab bacteria from mom's gut.

and take it to the fetus and pass some bacteria through the cord, through cord blood into the amniotic fluid. We

used to think back in the day that the amniotic fluid, cord blood, all of that was sterile.

Well, none of that is sterile, right? We couldn't culture organisms from it because all the organisms in there are anaerobic. And so we now know that it's loaded with bacteria.

And just think about the implications of Her immune system is taking bacteria to the baby. The immune system's job is to fight against bacteria and viruses and so on.

So if the immune system themselves is shuttling bacteria, there must be some great purpose for that. It just indicates how important microbes are And of course, the mode of birth has a huge impact as well.

Yeah, with all the C-sections. And, and I think too, that it kind of, when you have this abnormally, all the gut seems to calm down, the immune system are modulated and we're finding those are the kids who get autism, you know, the whole vaccine thing, but it's multifactorial.

But with, they have this immune system already hypervigilant. They're the ones, you know, that are more likely. have problems from whatever it is. It's an untrained immune system.

What we know now clearly about the immune system through lots of microbiome related studies is that when our thymus and our bone marrow makes immune cells, they really make very naive immune cells.

These immune cells then have to go to secondary lymphoid tissue where they mature and they learn how to function within this really complex ecosystem.

which is the body. They go into areas like the mesenteric lymph nodes, the adenoids, all of these areas where they get trained and a lot of that training happens with the microbiome.

You know, one of the crazy implications of the immune system when you really look at it is the inside part of the body is obviously covered with this amazing mucosal structure, right?

every square millimeter of the inside of the body is covered with a mucosa. In fact, there's almost 4,000 square feet of mucosa inside the body. It's a massive amount of surface area.

It's mind-boggling. We used to think the skin was the largest organ, largest barrier system, and the skin has somewhere around 20 square feet. of surface area, compare that to almost 4,000 inside the body.

So it's mind boggling when you think about it. And then every square millimeter of that mucosal layer is already covered in microbes, right? Bacteria, viruses, amoebas, protozoas potentially, we've got fungi, all kinds of stuff.

It's saturated. That is the area that the immune system is always surveying, right? So for invading organisms. So then the big question is, how in the world does the immune system survey this huge surface area that's already covered in microbes?

How does it survey it for microbes? If we're already full of bacteria and viruses, how does it actually do that? And when you look at the numbers, there's a 200,000 to one ratio for every one immune cell that you have that surveys the system, you have 200,000 microbes.

in that same area right so it's a mind boggling task for the immune system to survey that entire surface area. The only way the immune system does it is through crosstalk with the rest of the microbiome.

So the microbiome that exists in your mucosa acts as the neighborhood watch for the immune system. So the first organisms to identify the presence of a new pathogen or the presence of something that needs an immune reaction are the actual organisms, the commensal microbes around that area where this new organism comes in.

And then they shoot off flares to alert the immune system that, hey, there's something here, you need to come and

pay attention. So there's this really sophisticated- They're actually alerting the immune system.

Absolutely. Yeah, they're alerting their immune system. That's the only way the immune system can function. There are studies on no biotic mice, right?

So these are the mice that are grown with no microbiome, where the mice will produce all the immune cells that normal mice will. So the thymus is producing all the T cells.

They're producing all the B cells and macrophages. And then when they inject a viral pathogen into the mouse, the immune cells basically sit and stare at it.

They have no idea what to do, right? They have no training on how to approach that invading pathogen. The moment they implant in a microbiome and then do the test again, the immune cells go and attack that new pathogen because there are signals that come from the microbiome to instruct the immune system on how to operate.

So when you think about that, when you think of this really intimate relationship between the immune system and the microbiome, and if we are devastating the microbiome from day one in the child, from C-section, from not breastfeeding, from giving antibiotics, all of the different things we do, right, then that crosstalk, that communication between the immune system and the microbiome, ceases to exist the way it should.

So the immune system becomes confused from day one. It doesn't know what to attack, what not to attack, how to process through the immune, the immune response.

And basically either things will get not attacked at all. In some cases where people have severe immune deficiencies, kids have severe immune deficiencies or everything gets attacked, right?

Exactly. Oh, both. Yeah. And then, but all these allergies and autoimmunity, And then there's the, you know, the microbiome, you know, viruses and all these other things that we don't really, we know very little about.

And I read one study with the bacteriophage, which is the virus that kills bacteria. It was really interesting. It sensed, like, so one of the probiotics or, you know, one of the bacteria in the gut makes butyrate, which is good.

But if that level got to a certain point, it turned on the bacteriophage, which then killed that bug. Yeah. So it kept it from being too high. Exactly.

Yeah, the beautiful regulation. Oh my God. It's like you couldn't program a computer program to do that. No, you can't. It's amazing. And there's so many of these amazing feedback loops that we have within this complex ecosystem.

And that in itself will indicate that balance in the ecosystem is so critical to our function because there's all of these feedback loops.

Immune training, mucosal defense, and microbiome crosstalk

So let's say we eliminate one species from the microbiome or a group of bacteria from the microbiome. then all of the other microbes that are dependent on their function start to also get decimated over time, right?

And then we pay for it in the form of disease. Yeah, because it's also interconnected. I mean, one example I can give you is, we're all hypervigilant now about respiratory illnesses and viruses and all that, right?

Because of everything that's going on. One of the ways, for example, that our body fights against influenza, if we end up breathing in the influenza virus and it starts settling in the lungs, the lung microbiome will actually signal the presence of the influenza virus using upregulating things like inflammasomes to the gut microbiome.

And then the gut microbiome will then signal to the immune cells to make their way to the local area and then also send signals to dendritic cells to go to the local lymph nodes that support the lungs to proliferate T cells to come and fight the virus.

So there's this amazing communication between the lung microbiome and the gut microbiome to recruit and mobilize the immune system. And if one of those is compromised, then that chain of command goes away.

then you become so much more susceptible to the presence of this virus, right? So it's mind-boggling. It kind of reminds me like, well, ancient cultural, I think everything whatever comes from the gut.

Well, now that's crazy that we're right, you know? Totally, yeah. There's a certain amount of brilliance in that human intuition that's been built over thousands of years, right?

That You know, we know even the father of modern medicine, right? Hippocrates said that death sits in the bowel and most disease comes from this digestive issues, right?

So, yeah. And it's, you know, I tried to take a deep dive on, okay, I'm going to figure out, you know, which probiotics I need. Oh my gosh, it's so difficult because like so many studies use multiple strains and this study shows this.

Like, how the heck do you figure it out? Yeah. You know, It's so hard. And when I started 10 years ago, specifically focusing on probiotics, that was a big part of what we looked at is, what are some of the key fundamental things that we find to be dysfunctional across most people's gut in the Western world that we really need to address?

And that's kind of what we honed in on because you can find different probiotic strains for different effects in the body and that will just get bigger and bigger and more confusing over time.

But we were thinking more fundamentally what do we need to fix as root cause, as part of the root cause medicine approach. And there were a couple of things that we realized, three things really that we really realized that needed to be done.

Number one was improving diversity within the microbiome. Because again, that mass extinction is happening where we're really losing huge categories of bacteria.

And that has real effects on our outcomes. And that's transgenerational. Because as we decimate our microbiome, we pass down a decimated microbiome to our kids.

Theirs get even worse, and they pass it down. those genes and you're, we're finding now, you know, we're doing genetics, but your genetics actually play less of a control over your outcome than your environment, your microbiome, because it matters if that genes turned on or not.

you can have it, and two people have it, but one person is turned on, one person is turned off. Yeah, exactly. And, you know, what we come to find out is there's good evidence that the microbiome makes up for a lot of our SNPs that we may have, right?

For example, if you're somebody that struggles with a, you know, methylation SNP, is that detrimental to you if you have a microbiome that produces all of these methylated vitamins, or does methylation itself, right?

So it seems like there's this really interesting relationship between our own genetics and then the microbial genetics that exist, where the microbial genetics provides us some redundancies and function.

Yeah, hey, I don't have it, but I got these guys to do it. Exactly. Yeah. And if we miss these guys, then all of a sudden that SNP becomes a real problem, right?

MTHFR can become a serious issue for people if they don't have the microbes to make up for it. So those kinds of things occur nonstop within the system.

And so this loss of organisms and loss of function from the microbiome is really a scary track that we're on right now. So we said, okay, improving diversity is critical.

We tend to have this overabundance of pathogens just because of our lifestyle, because of the use of antibiotics and the overuse of antibiotics, the use of them in our foods and water supply, all of these things.

tend to select for an overgrowth of pathogens. So one of the characteristics that we have in the Western world is an overabundance of certain pathogens and a low abundance of really important functional strains.

And so that was one of the issues of diversity we wanted to fix. The second issue that we saw was the low abundance of keystone species. Keystone species are about a handful of species or so within the microbiome that have been identified that play a really critical role in maintaining the ecosystem of the microbiome and also servicing something called crossfeeding across many different species and groups.

So you've got this one keystone bacteria that supports a huge array of other bacteria from the metabolic activity that they perform. And when you lose that keystone bacteria, you start decimating a lot of the other bacteria that depend on it.

Now also certain keystone species are really critical for maintaining function. So I'll give you an example, acromansia mucinophila. Acromansia mucinophila is inversely correlated with everything under the cardiometabolic syndrome spectrum.

But you can't take that directly, right? You can't take it directly. It's a gut-only organism. It's an obligate anaerobic, meaning it cannot exist outside of the body, even for a few seconds.

And they've tried doing implementation or implanting with killed versions of acromansia. And the killed versions of acromansia don't do anything in the system.

So you need live functioning acromansia. And when you have high acromansia, it brings down dramatically the risk of diabetes, heart disease, obesity, polycystic ovarian, Alzheimer's, all of these things under that metabolic syndrome spectrum.

So that's an example of a keystone strain. And in the Western world, we tend to have low levels of these critically important protective keystone strains.

So diversity, keystone strains, and then the third thing, which actually results in the first two. How do you raise that? So that's part of our product strategy and lifestyle change strategies.

So we can talk about that. I'll list the third one, and then I'll give you how we approach dealing with all of them. So the third issue that we look to solve, which actually is a factor of the first two, is leaky gut.

Leaky gut becomes the underlying profound problem that stems from having low diversity and low keystone strains, right? And then it's a vicious cycle.

And as you know, leaky gut then becomes really the foundation for most chronic illnesses, including things that affect the brain. One of the most toxic things for the brain is leaky gut endotoxemia which we could chat about how the dysfunctional gut really feeds toxicity to the brain, but how we address the first two things.

That's kind of why we honed in on the spores you know we use the mega spore biotic is what we work with, we do all our clinical studies with. The spores were interesting because they are ubiquitous organisms in nature, but then there are also normal commensal organism in the gut.

Spore-based probiotics and restoring gut balance

In fact, you find higher concentrations in the gut than you do in nature, which is indicative that these organisms use

the environment as a vector to get into the host.

and they are universal colonizers because I didn't get a very particular type of bacillus from my mom. I actually got bacillus from the environment. You picked up the same bacillus from the environment as I did.

Most other species within the gut microbiome are unique to us because we got them from our mom, she got them from their mom, we got them from close interaction with our mom and dad.

Most individuals, when you look at their microbiome at the species level, they have a different microbiome. even identical twins will have up to 50% differences in their microbiomes.

But there are certain organisms that are called universal colonizers because we all pick them up from the same source. The spores were one of them. When we started digging into the spores because of their ability to survive through the gastric system and all that, we found that a couple of big pharma companies had launched them as prescription probiotics since 1952. And so they've been in the market for a long time and they're used to treat gut infections because they have this unique capability of going in the gut, doing something called quorum sensing, where they read the microbial environment.

They can find overgrown or pathogenic organisms. They will sit next to them and they will actually bring down their levels by producing things like antimicrobials and all that in that local area.

Once they change their secretome. Yeah. Absolutely. We've got some bad bugs here, we're going to get rid of them. We're going to get rid of them. We actually did a study with Cleveland Clinic on C.

diff, where we wanted to study how do the spores actually fight against C. diff, and it's absolutely fascinating. So what we were able to see, and this study actually has been published now, what we were able to see is when the spores enter the gut, they will actually find the C.

diff bacterial colonies they will go and they will actually surround the C. diff colonies and they will chelate iron away from the C. diff. And C. diff requires iron for metabolic function.

If it doesn't have iron, it dies off. So it actually changes its genetic expression and produces a chelator and pulls iron away from C. diff to kill it off.

It's like the best employee you've ever had. Exactly, right. And it goes the other way, too. And I was reading some studies on C. diff patients, no matter how many antibiotics.

And I saw that camphorlobacter dejuni, which they say, well, it's kind of there, but it's not terrible. But if you kill that, you kill C. diff and also Pseudomonas, which is another bacteria.

So certain things need certain things to live. But that's incredible. Yeah. And so their ability to do that is really mind-boggling. And so our hypothesis was that if the spores knew how to figure out what bacteria shouldn't be there, maybe they also know the opposite.

They can realize what bacteria should be there, and maybe they have tools to actually increase the growth of those bacteria, right? So that was our hypothesis.

And sure enough, we publish now at least one study. We have a second on the way publishing that demonstrates that, that when you add the spores into the microbiome, they actually increase the diversity of the microbiome, because they can bring down overgrown and unwanted microbes, and then they produce compounds to actually increase the growth of other functional bacteria, including the keystone species.

And so we see… I think you just get all those that you're giving, but if not, you're getting all the other good ones as well. You are, exactly. So that was really profound for us.

We said, wow, that is a huge implication to what it's doing in the gut because it's fundamentally changing what the microbiome looks like. So we're not counting on just their effect, we're counting on their ability to influence the rest of the microbiome.

So you see a product with 50 of them, oh, this one's better. And which I have a doubt that many of these F1 make it through the gut. Right. And they don't.

And like the liquid ones, okay, the refrigerator, yeah, they probably shipped them non-refrigerated, you know. And that's why I think the spores are really the way to go.

In terms of like modulating the microbiome, it's that the right way to go. And then when you look at the ones that have 25, 35, 40 strains, it sounds like a lot.

But the problem is that's typically of a single genus or maybe two genuses, right? It's like 20 different lactobacillus strains and maybe 10 different bifidobacteria strains.

So that only covers two genuses in the gut microbiome. Your microbiome could have anywhere from 150 to 200 different genuses. So what about all of those other microbes?

You're not really expanding diversity in any measurable way. And so we were looking at it from a different perspective. And we said, OK, we can increase diversity with the spores, we can increase keystone strains, we can bring down pathogenic organisms, which is fantastic.

Does that lead to alleviating the third problem, which is leaky gut? That would really be the impact that we're looking for ultimately. Sure enough, we published our first study on this in 2017, showing that in as little as 30 days, the spores reduce intestinal permeability by over 60 percent.

I met you in Hawaii and you gave that study and I'm like, damn, yeah. Which is crazy. It's right there, third party, you know. University done and published in a major gastroenterology journal.

And the awesome thing about that is, yes, we were able to reduce intestinal permeability. We were able to reduce LPS, which is the lipopolysaccharide endotoxin that's produced at high amounts in the gut, in the lumen that then moves across the barrier because the barrier is dysfunctional, into circulation.

We were able to reduce that. But the even more profound effect is we then saw all of the benefits from reducing the permeability. We saw this huge modulation of systemic inflammation.

the people on the spores compared to the placebo had a huge drop in all of the critical inflammatory cytokines like interleukin-6, interleukin-1-beta, interleukin-12.

They started to see an increase. And that's the cause of so many things we're finding out. Heart disease, cholesterol, it's not cholesterol, it's inflammation.

Yeah, exactly. And that's a foundational thing, right? Even now, there's something that just published a couple days ago called the, it's called the Dublin, I think it's called the Boston Dublin Score on COVID.

There's this research group between a US university and a university in Ireland that has been, what is it? No, I'm just guessing that whatever the information you start with, is going to put you in trouble.

That's my guess. Oh, right, right. Yeah. In terms of what we're saying, you mean? No, I'm just guessing what the outcome is going to be. Yeah. Oh, yeah.

So it was mind boggling because they put out this index or the score to try to assess which patients would have the worst go at run with COVID. And what they found was very clear that if the individuals had elevated interleukin 6 and low interleukin-10, then they had a much worse go at COVID.

If they had the reverse, lower interleukin-6 and elevated interleukin-10, they had a much easier go with the disease, right? So the baseline of where their inflammation is really determine how well their immune system worked and how well their body dealt with all of this.

Essentially, you look at a few markers and say, if you're at risk or not, we're looking at all these different things where you can boil it down to one mark.

have a treatment, you know? Well, totally. And that's the idea is that the, you know, when you look at interleukin-6, that is the quintessential systemic inflammatory marker, right?

It is present in all of these chronic illnesses. That's the big problem with COVID too. That's the big problem, exactly. That's why people with certain pre-existing conditions have a much worse go.

These are conditions like diabetes, obesity, hypertension, heart disease. All of those are characterized by elevated interleukin-6, right? So they are starting at that bad stage, and then that is going to create a profoundly bad experience with this particular pathogen.

And then the big issue here is that leaky gut is the big driver of this systemic chronic interleukin 6 elevation. It's what they call the chronic low grade inflammation, right?

So that exists in large part because it's being driven by endotoxemia or leaky gut. And so, you know, when it comes down to it, just looking at being able to modulate the microbiome, modulate the leakiness in the gut has profound impact on people in general, whether they're looking at a crazy pandemic that's going around, or they're looking at all of the chronic illnesses that American adults are facing and dealing with all the time, right, 60% of which are dealing with it.

So that was our whole approach, the idea of the microbiome probiotics, you know, and then coming back to the brain, this LPS, in circulation is one of the most toxic things to the brain.

When LPS is allowed to leak from the lumen of the gut into circulation, it gets into all kinds of crevices in the brain, right? So studies show, for example, in a paper published September of 2017, showed that the inflammatory process that starts the degeneration in the case of Alzheimer's in the perinuclear region of the brain, what they found was a thing that started the inflammatory process was a presence of gut-derived LPS.

Leaky gut, inflammation, and brain health

So people who have the early signs of Alzheimer's pathology starts because gut derived LPS leaks through, goes up either the vagus nerve or through circulation into the brain and starts triggering an inflammatory response in the brain.

You know, same thing happens in Parkinson's. They find that LPS in the central nervous system creates microglial activation that starts the process of neurodegeneration, right?

So the gut-derived toxin that we can't get away from, because it's called an endotoxin, it's made on the inside. If that's allowed to leak through, it becomes the most toxic thing that- Let's, you know, have some ALS patients, you know, and same thing.

They all have leaky gut and associated with particular pathogens and it seems to start everything. And then though it seems like a vicious cycle, the brain also controls the gut.

So if you fix the gut though, does it, let's say you fix the gut, does it tend to go back to where it was because the brain is dysfunctional? So like a two-way thing.

Yeah, it can. And one of the biggest ways that the brain can impact the gut is really the sympathetic, parasympathetic tonality. If we tend to be more often in a sympathetic state, that actually creates a release of

stress hormones, things like epinephrine, norepinephrine, cortisol, One of the things that occurs when those hormones are released is that opportunistic bacteria and viruses within the gut and within our system in general, they read those signals.

To them, that means the host is compromised. That's when they turn on their virulence genes, right? So our brain response, our sympathetic response can create further dysbiosis in the gut and overgrowth of pathogens.

which completely changes the metabolic response in the gut. And then because the opportunistic microbes are overgrowing now, they create more inflammation and more leaky gut, that actually drives more dysfunction in the brain.

So it's like a vicious cycle, like you said. And some of the other things that LPS can affect. So we know that LPS can get into the amygdala and the hippocampus in the brain.

It triggers inflammation in the amygdala and hippocampus and has been demonstrated to cause memory recall issues, cognitive functions, the ability for the slowing down of analytical capability in the brain, that whole brain fogginess.

LPS can also inhibit serotonin binding and dopamine binding in the brain, which And anger, exactly. And compromise the whole HPA axis, the hypothalamic pituitary adrenal axis, right?

Yeah, so all of it. I mean, it's mind boggling when we think about how we're seeing earlier and earlier onset of issues like anxiety and stress in kids, in our teenagers.

Of course, there's lots of things in the social world that drive that, right? But their guts are decimated and it's making them more susceptible. almost every study I've seen with like, you know, just across the board, all these new diseases, whatever, you know, are help with improving the gut.

Totally. And even things like the military has studies on leaky gut and then post-traumatic stress, right? So what they've shown is that when you put soldiers through basic training, the stress associated with basic training, the poor nutrition, the conditions, the lack of sleep, all of that actually causes more intestinal permeability.

And when the intestinal permeability is high, after basic training, then they put them into stress areas like combat zones and all that. It makes it really hard for them to deal with the stress.

They become far more susceptible to post-traumatic stress, right? And all of the other emotional conditions. And their gut gets worse because they have post-traumatic stress and then, yeah.

It's crazy. It's crazy. So, I mean, we, we cannot overstate the importance of the gut and we cannot overstate the importance of focusing on the gut along with the other therapies, you know, things, awesome stuff that you guys put together and make all of these things will become, will, will be much more synergistic and work in a, in a much more profound way.

It all works together. We used toning and probiotics and And that's things like, you know, I was on a SIBO thing and I said, well, I think SIBO is more of a symptom, you know.

Well, it's both. It's a marker. It's a symptom. It's because, you know, the guts dysfunctional because they have some other issue going on, but you got the other issues going on because you have the gut problem.

Right. Exactly. So what do you do? And what, you know, you find like, you know, certain, like I say, wait, you know, like over obese patients have this particular microbiome.

And so they've tried to, you know, switch it and give a lot of this hasn't been as successful as we had hoped. Can you comment on that? Yeah, we actually have a study completed that finished at the end of last year.

We're hoping it'll be published soon showing something that we call metabolic reprogramming, right? The whole idea was that when you struggle with weight and metabolic disease, you have a certain signature within your microbiome.

those that tend to remain lean and never struggle with weight in their life have another signature, right? So the idea was, can we do things to switch the signature of your microbiome without dieting and exercise and all that yet, and start to see improvements in how your body responds to food, right?

So we're doing, again, a foundational fix before we do all of the things that are difficult for the person like dieting and exercising and all that. Because right now we know that dieting and exercise will get you to lose weight.

We know that restricting calories, burning more calories will get you to lose weight. But then the biggest struggle is people can't keep it off because their microbiome is still that of an obese individual, right?

So their body responds to food differently. So we did this study where we looked at the fundamental differences. There are really three big things. One is an increase in acromancia, that same keystone strain.

We need to see an increase in bifidobacteria, especially bifidobacteria animalis, within the microbiome. And we need to see an increase in the production of short-chain fatty acids, especially butyrate.

So those three factors will determine in large part what your body composition looks like and how you respond to food. And so in the study, what we did is we took two of our spore strains, the subtilis and the coagulans, and then we took a prebiotic, a xylooligosaccharide.

Between these three, we knew that they would feed acromansia, they would feed bifidobacteria, and they would increase the production of short-chain fatty acids.

What is the name of your product, that product? So we haven't named it yet. It's because we were still going through the clinical trials. But the two strains that we use are two of the main strains in Megaspore.

So you can get the same effect by just taking the Megaspore. And then we have a product called Megapre that has four different oligosaccharides. For the study, we only use one of the four.

So if you do the Megapre, you'll get more than enough of the prebiotic effect. So here's what we did. We took obese individuals and this was all on women.

So the control measures are a little bit better if you keep with one gender. We didn't have them change anything about their diet. We didn't have them add in or do anything different with exercise.

And we used DEXA analysis to look at body composition, fat change. We looked at things like C-peptide, insulin levels, triglycerides, all of that. And we did a 90 day study where all they did was took the probiotic and prebiotic and didn't change anything else, right?

This was a smaller pilot study. I think we had about 20 patients, just under 20. But just tell the people, you know, listen, these are not cheap to do.

No, oh my god. Yeah, it's a patient study of this caliber for 90 days in itself is like $400,000. Yeah. So I mean, you guys are putting that's a huge amount of money put back and you guys are doing that constantly.

We're doing that. Next leaky gut study has over 200 patients in it. We're really investing in research. Nobody's doing that in the probiotic space. Part of it is because we really want to make discoveries.

We want to find ways of helping people like yourself and all of these healthcare practitioners that are out there, you know, fighting the good fight. We want to give them the best tools to be able to do that.

But what we saw that was fascinating in this study is in the 90-day period, remember these people are not doing any dieting, not doing any exercising.

They're still living the lifestyle that got them obese in the first place. And so what we saw in that 90 day period was that the people on the probiotic and prebiotic lost 12% of visceral fatness, right?

Huge reduction. Say that again? In what period of time? In a three month period. 12%. It's insane, right? And it's all visceral fat, most of what they lost.

So it's the most dangerous fat. And then the placebo group, because this was a randomized control trial, the placebo group obviously didn't lose anything.

They gained 11%. As soon as someone you say diet or anything, it's like, I can't wait. I want to diet, I can't wait. So when you compare the two, the difference is huge.

Now, the other things that we saw that were really exciting was things like C-peptide and insulin levels would change, meaning that their bodies were producing less insulin over that three-month period than the placebo group.

So their insulin spikes were not the same as well. we also saw triglyceride levels coming down. So the liver and the liver fat and the fatty, free fatty acids in the circulation came down quite a bit.

Yeah. So their insulin resistance went down. They didn't have, because people think, oh, your doc, standard doctors look at their sugar level, but their insulin level is crazy.

Totally. It's telling the body to store fat. So the fact that those patients had low insulin and lower sugar, That's huge. That's huge. And so, and again, without any lifestyle change, and what it's showing is that because we're making a change in their microbiome, their body is responding differently to food, right?

So now the idea is that, okay, you start making that fundamental change in the microbiome, you add upon that some minor dietary changes, some little bit of addition of exercise and movement, you know, increase it over time.

Think about the profound change we can make in just a little difference. So I think if people lose weight, they get more motivation because people have tried to lose weight and it doesn't work.

So I got a business proposition for you. put it in a packet for a beer, we can put it in beer. Yeah, exactly. That'd be an easy way to consume it. Absolutely.

But yeah, what was exciting about that to me and our big purpose of doing that study was to prove our hypothesis that we could metabolically reprogram the individual.

That by changing certain signatures within the microbiome, we could actually change how your body responds to food. And it totally does, right? When's that coming out?

So the study is done. It was finished at the end of last year. We're hoping to have it published, hopefully, in the next three or four months. We did this insane RNA BLAST study, too, to look at the metabolomics of all of the things that change in the individual, too.

No, and that's super complicated. I mean, we looked at hundreds of thousands of RNA molecules. And the computer programs, looking at stuff. Totally. And the computation needs for that are mind boggling, right?

So we're running through some of the RNA analysis still. That's taken like nine months to do because of the amount of computational needs that it has.

But we're really hoping to have that all put together and it'd be published sometime early next year.

Metabolic reprogramming through microbiome support

If you have any pre-publication, I'd love to see it. Yeah, I can send it to you. Absolutely. I can send you a PowerPoint of it. That's fascinating. It's mind boggling that we could do that.

And again, it speaks to the power of the microbiome, that if we can make small changes in the microbiome, the effect on the individual is really profound, because we're just tweaking little things.

And I think we can do that with virtually every condition out there. how much money we're spending on all these Alzheimer, COVID, you know, we're waiting till they're so sick.

It's almost, and that's why I talk about peptides. I take it early and there is some shift by some physician, but we're all minority, right? Is I was just thinking, what if we take your product and give it all to nursing home?

You know, what would the death rate all of a sudden be? You know, probably drop dramatically or just give them zinc and you know, it just, but we don't work that way.

We don't, yeah, unfortunately. And then, you know, and the whole thing is like the disease doesn't exist until it's really apparent, right? We have no way in modern medicine to grade stages of the disease, right?

Somebody could be in autoimmune syndrome, meaning they're moving towards a defined autoimmune disease for a decade before lupus shows up or before rheumatoid arthritis shows up, but we have no way of measuring that progress and stopping the disease at an early stage.

It would be so expensive to do such a long study to show we prevented this, this, this. Exactly. Who's going to have that? You're pumping a lot of money back into your thing.

That's awesome. How does what we eat, how does that affect? That has a profound effect on the microbiome. What we eat can change the microbiome within a 24-hour period or at least change a portion of the microbiome within that period.

The biggest issue that I see when based on the research, between what's going on with our diet today and what happened with our diet through the course of evolution is the diversity of things that we eat, right?

So anthropological studies show that humans typically ate close to 600 different types of foods on an annual basis. And our modern humans now in the Western world, we might eat 15 different types of foods.

And the way the diversity in our microbiome developed was every group of bacteria kind of feeds differently off of different foods. And each food has its own different structure and bonds and all that.

So each bacteria has developed their own unique enzymes to be able to metabolize different food sources, right? So even when you look at within a certain category, if you look at roots and tubers, sweet potato is going to feed a different type of bacteria than the regular white potatoes that we're used to, because the structures, the carbohydrate structures are different enough.

Right. So that is one of the big areas that we are really lacking. And then everything's processed. So taking out all that other stuff where the bacteria used to live and everything's sterile now, you know.

We're not getting microbes in our food. Absolutely. And, you know, I mean, the basis of most of our foods and meals, especially if people are eating processed stuff, is really comes down to soy, wheat, That's really most of what it is.

More than 85% of Americans get all of their fiber from wheat, right? It's in everything. It's in everything. It's not even wheat-based. Yep, exactly. You look at spices, you know, like you might think I'm going gluten free, right?

But you look at the spices in your cabinet, the carrier is wheat flour, right? And you're getting gluten and wheat through that. And so it's really a big issue, the diversity in the diet.

And then overfeeding, you know, that's another big issue. So we're not doing enough fasting. We're not giving our bodies enough for a period of time. Yeah.

So, you know, that's another issue that we have to deal with. We're overfeeding the microbiome. Wow. And is there any issues? Can you take too many probiotics?

Yeah. So one of the things that keeps me up at night a little bit is these, what I call the kitchen sink probiotic approach, right? Where it's like more is better behind the psychology of it.

Where you do 15, 25 strains, 400, 500 billion, 200 billion, the doses just keep going up and up. The big problem with that is, you know, we talked earlier how important the gene pool is within the microbiome, because the gene pool dictates so much of our functionality.

If we're throwing 200 billion CFUs worth of genetic, bacterial genetic elements into our microbiome gene pool each day, over time, we are accumulating a very different set of microbiome genetics.

Even if those bacteria don't survive, even if they're dying the stomach, they're releasing all of their DNA into our microbiome. So how does that DNA impact the function of our microbiome over time?

And people don't study that when they produce these kind of kitchen sink probiotics. So to me, that becomes a little bit of a concern because we may be inadvertently altering what our microbiome is supposed to look like over time, because it's not natural.

There isn't anywhere in nature where you would get these types of 20-25 species lactobifidal combinations at that high of a dose every single day, right?

Our ancestors didn't do that. You don't find that in the natural environment. You don't find that when you eat off of the land and so on. So it's an unnatural exposure to those category of bacteria.

So to me, the difficult thing is what does that do to the microbiome over time? And with probiotic companies not really doing studies, you really have no idea.

Yeah, there is. I'm glad you lost sleepover because I tried. I'm going to figure this thing out. Weeks of not sleeping. I'm like, oh my gosh, it's hard.

Can you talk about the difference, you know, the genus and the strain there, you know, how important is the different strain and what's the difference between genus strain?

Absolutely. So when we look at bacteria, we of course can categorize them between genus species and then there's the subspecies within the species. Typically, the subspecies is identified by a unique strain number.

So we take, for example, lactobacillus rhamnosus, the genus being lactobacillus, the species being rhamnosus, but then there are new variants of rhamnosus like the GG variant.

that has a number of studies on it. And when you look at the genetic map of a regular rhamnosus versus a GG variant, they can have as much as four or 5% differences in their genetics.

So even though it's a rhamnosus by category, performs differently, yeah. It's like more than us and an ape. An ape, absolutely, right? And so what's really important about that is when a company does studies on rhamnosus GG and shows these beneficial effects, the assumption in the industry is, oh, look at these rhamnosus.

Yeah, I'm just going to take the cheapest rhamnosus and claim that I have the same effect. But it doesn't, it's super

strain dependent. Same thing with Bifidobacterium infantis 35624 or BLP1, all of these different subspecies have their own unique effect.

And it's absolutely clear from studies that you cannot translate that effect to a normal version of that strain. And most of what is sold in the market are the normal generic versions of these strains.

You know, I've had conversations before with people in the industry and they say, you know, well, there's lots of studies on lactobacillus rhamnosus. So why do you say the products on the market don't really do anything?

But my response is, well, there's lots of studies on rhamnosus GG. But when you look at the number of products that are using that variant, it's minuscule compared to the number of products that are using the most generic cheap version of Ramro.

People say, look, we're the same as Megasport. Yep, exactly. And it's not. You have to have the right species. And without actually testing the formulation, in both humans, in gut models, in animals, you really have no idea what it does in the system, right?

So one of the other things that is a bit of a pet peeve for me in the probiotic industry is companies will put together products and they'll say clinically validated or clinically tested.

What they mean is two or three of the strains that they have have clinical trials independently, right? So they have clinical trials on this strain by itself, on this effect, and then they have clinical studies on this strain by itself, and then they'll combine them together with a bunch of other stuff and assume all of those effects are still there.

You can't do that. That's a major leap, right? Because you don't know what's going to happen to those microbes when you combine them and put them into the system.

They're living organisms. And so that's another part that kind of the industry tries to pull the wool over people's eyes by seeming like they are well-researched when really what they're doing is pulling to these other things.

Look, we're the same. And just kind of lastly, any particular gut tests that you recommend? Yeah, you know, I worked a lot with gut tests over the last few years because I was really unhappy with what they're offering as gut tests in the marketplace at the moment for a couple of reasons.

Number one, all of these gut tests on the market use technology called 16S ribosomal RNA sequencing. So the problem with 16S sequencing is that it cannot identify bacteria down to the species and definitely not to the subspecies level with any accuracy.

It's pretty good at identifying bacteria to the genus level, but not to the species level. It can tell you lactobacilli is there, but it doesn't tell you which lactobacilli is there and in what amount.

So that's really problematic because when it comes to the microbiome, What matters is what species are there and what is all of their relative abundance, right?

You have to understand the whole ecosystem and map out the whole ecosystem to understand what functions are missing or what functions tend to be overrepresented in the microbiome.

So that was the first issue is that using the 16S sequencing. The other issue was most of the tests on the market are heavily focused on pathogens.

Diet, probiotic strain specificity, and microbiome testing

Most of what they test and show you is where are these pathogens in your gut? And the problem is, number one, in most cases, these pathogens aren't necessarily causing the problem.

It depends on what the rest of the microbiome looks like, right? Pathogens exist in everyone's gut. That's a given. They are a normal part of our commensal flora, like Clostridium difficile is going to be there in most people's gut, right?

Salmonella, most people's gut, Klebsiella, everyone has these. within their microbiome. The question is, what does the rest of the microbiome look like?

Because pathogens are only a problem when the rest of the microbiome is diminished. I picture those surrounding them. And we call that our pathobiome index.

So it really tells you whether or not pathogens are an issue. So because these tests are just heavily focused on pathogens, and they give you kind of this arbitrary high and low reading of pathogens, What it tends to do is make people look at a microbiome test and go, oh crap, I've got high levels of this pathogen and that pathogen.

Well, what are you going to do about it? But take a bunch of antimicrobials all the time, right? There's no other solution to it. Exactly. And the antimicrobials, even with the natural ones, are going to kill off good and bad bacteria.

They're not hyperselective just for bad bacteria. So more often than not, what we found in looking through all of these tests, interacting with the clinicians we work with, with the patients we work with about these tests, is these tests aren't really telling you much about the microbiome.

And it's not giving you opportunities to find areas of healing. Right? And so what we decided to do is we came up with a completely new way of doing the microbiome.

What do you do about it? Yeah, absolutely. Because what we said is, okay, there is better sequencing technology than 16S, right? And it's called whole genome sequencing.

Whole genome sequencing can give you absolutely accurate identification down to the species level. So already we made a big improvement saying, we're going to use the best version of the technology to give you accurate results.

Then the second part of it is really mapping the microbiome, because it doesn't really matter who is there. It matters who else is there. So the ecosystem is critical.

So what we did is we worked with the most preeminent researcher in this space for microbiome mapping. Her name is Rita Caldwell. She's got over 800 published studies.

in this space, she's received, yeah, she has 60 honorary degrees, right? She's got a couple of her PhDs of her own, but 60 honorary degrees on top of that.

She's won, you know, Medal of Science, the highest recognition of science from President George Bush and a number of, you know, massive accolades like that.

She is the go-to person for this. So we work with her and her team to figure out how to map the microbiome so we can give you real ideas on the functionality of your microbiome.

So what our test focuses on is the functionality and what does the ecosystem within the microbiome look like and what does that ecosystem convey in terms of function and symptomology in the patient.

And so, and everything we test for we provide actionable steps. Everything has a diet, lifestyle, supplement, actionable steps so that you can do something.

So what's the name of that? That's called BiomeFX, B-I-O-M-E in the letter F and letter X. It's a full functional microbiome analysis that really talks about functions and mapping within your microbiome.

And again, everything's actionable. Physicians and patients or through physicians? Yep, just through health practitioners for their patients. Can you say it again and where a website?

So you can go to the website biomefx.com or through our own website, microbiomelabs.com, you'll find it on there. Yeah, and if you just Google biomefx, you'll find it as well.

But what's so exciting about it, and we've now done a few thousand tests already We've got lots and lots of clinicians that now use it regularly as their preeminent test is that it really provides you somewhere around 37 different functionality analysis of your microbiome.

So it gives you an understanding of what your microbiome tends to do a lot and tends not to do very well, you know, and that's how you kind of adjust your approach to the most important things to start to fix.

Oh, that's great. And I asked because I've done a lot of these. I'm like, OK, it's helpful. But I haven't done that. So we'll start ordering. Yeah. Yeah.

I can't wait for your feedback on it. We've got nothing but awesome feedback on it. And it's really providing insights for clinicians into what's going on with their patients.

And it really provides you a number of healing opportunities for them. That's great. I think it was just fascinating. This is just one of the best talks and really got down to, I think, just the core and the key to the, to the gut and really how important it is.

And, you know, just, just, just, just right to the core of it. So, yeah. Yeah. And I just love, you know, you're so research-based and. and knowledgeable.

I mean, you know, everyone's like throwing around probiotics like crazy. And I think you make people feel comfortable. So it's like, this is the one you got to go with.

Yeah. Thank you so much. Yeah. So thank you. I mean, it was just, I am, I, I'm blown away. So I think it's great. I've read. Again, the one study you did, looking forward to the other ones and just how much knowledge and just good research, because there's so much stuff out there, but it's just all over the place.

It is. It is all over the place. And ultimately, it's about making it simple, accessible, both for clinicians and then their patients. I mean, clinicians have so much to learn and deal with that it's so hard for a clinician to spend their time grappling this concept of the microbiome.

when you're spending most of your day dealing with patients. I tried to find the perfect probiotic. I almost went crazy. Exactly, yeah. Thank you, Burt, for coming up with to do it.

Absolutely. And we call ourselves Microbiome Labs for that reason. It was our mission to make sense of it and provide tools that can really make changes in the microbiome.

So we're excited to continue the work we're doing. And thank you so much for the support. Hey, thank you so much for being on. I think this was this was great, so informative, and I appreciate you taking the time.

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