Build Your Resilient Gut
MICROBIOME & BEYOND

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MODULE 3 - Video Transcript

Introduction + What is Leaky Gut:

So leaky gut endotoxemia. Now, there's slight difference in how we use the terminology, but they're, in a way, one and the same. In fact, it's a progression, right? Leaky gut leads to endotoxemia. To give you guys a more functional version of the definition, so you have the right terminology here, so leaky gut is the, of course, generic term for intestinal permeability or barrier dysfunction, right? And we'll go through why the gut is a dynamic barrier, and how that's structured, and what does leaky gut really look like when you lose the dynamic nature of the gut barrier?

But the result of leaky gut is this process called endotoxemia. To break down this word, do endotoxemia really is the prefix endo means that it's a toxin that's generated from within. We'll cover that, which is LPS. So as opposed to an exotoxin, the one that comes in from the outside. So it's an endotox, emia means it's now in the blood, right? Emia, the suffix is that it's now something that is manifesting itself in the blood. So endotoxemia is the consequence of leaky gut, and it's the most important clinical consequence of leaky gut. So often, when people say, "What is leaky gut?" Well, it's really increased intestinal permeability, right? And it's an increase in intestinal permeability, and it's a loss of control of permeability, because the intestines are really supposed to be permeable. So leaky gut is an increase in permeability and a loss of some of the governance around permeability.

It's not just that the gut is leaky or not leaky, right? And that's a common misnomer, where they say, "Well, we're going to seal up the gut and stop the leakiness." What we really mean, when people are referring to that, hopefully what they mean is that they're going to reduce the uncontrolled permeability part of it, because the intestines, especially the small intestine, and to some degree the large intestine, is supposed to be permeable, but in a much more dynamic fashion. Now, when it has uncontrolled leakiness because of physiological changes to the barrier, what you then get is you get

things like toxins migrating through, bacteria, viruses, bacterial byproducts, food components, environmental toxins, all of these things leaking through where they shouldn't be, and when they leak through, then they have a chance of entering into circulation.

Now, a lot of it, when it leaks through, ends up going through portal circulation, which goes to the liver, which is part of the reason why the liver takes a huge brunt of the impact and toxicity from leaky gut. And then, a dysfunctional liver perpetuates the problem, and I'll address that a little bit as we go along as well. But ultimately, what you end up is a lot of inflammation, not only at the source of the leakiness, and I'll explain why that happens at the source, but then systemically as well. So remember, the gut is supposed to be leaky, it is supposed to be permeable, but it's a degree of permeability and the ability to govern or control what comes through and what doesn't. It's a loss of that or a reduction of that that really makes a difference in this condition, right?

Lesson 1: The Mighty Mucosa

The really important part of the barrier system of the gut lining is this segment called the mucosa. Now, the mucosa and the mucous or the mucin are two separate things. We often talk about it as one, just it makes it easier to understand it that way. But given that you guys are in a class, learning things in the most frank way possible, I want to give you the most specific definitions. So the mucosa, and I'll have a diagram of this in the next slide, is the entire barrier system of the gut. So it's actually the mucous layer and then the epithelial cells, the basolateral, which is called the lamina propria, and then there's a muscularis as well, which is the smooth muscle cells that control contractile movement, and peristalsis, and so on. So that entire structure is actually referred to typically as the mucosa.

What we're usually referring to where the microbes live, and things start to penetrate through, is the mucin or the mucous layer of the gut lining, right? So keep that in mind.

So we'll use the terminology somewhat interchangeably, but I'll try to be specific, so you guys are very aware of what we're actually talking about. But the mucosa is really the defense mechanism, and it's a very dynamic system, as we talked about, and the very front layer of the mucosa is this mucous barrier. So there's this mucin-mucous barrier that acts as a defense mechanism. It is around 4,000 square feet, so about 400 square meters in the gut, so it's a huge surface area. A lot of that surface area comes from how the small bowel's physiology is set up. You'll see that in the next slide, but it's a massive surface area.

Imagine in your digestive tract, in this small area here in your midsection, you've got almost 4,000 square feet of surface area. The other thing about that surface area is there's a lot of space for things to go wrong. So imagine if your mucous barrier, your mucosa starts to get dismantled in this given region, that's all folded up here. Even if a 10th of it becomes dysfunctional, right, you've got 400 square feet of the 4,000 that becomes dysfunctional, it can really have a huge impact, and then that becomes a perpetual problem. So you've got an entire tennis court or professional basketball court folded up in here. Every single square inch of that area has to have the proper structure and the proper functionality, and it's not very hard for that to start to get dismantled.

So it's got that mucin layer that I talked about, the very top. So you've got the epithelium, and I promise you, I'll show you a diagram next, because it's easier to see it and understand it when you can visualize. But you've got the epithelial, which are the barrier cells of your intestines. Sitting on top of the epithelium is this layer of mucin, right? That's the mucus part of it. The mucus part of it is not just nonspecific mucus. It's a very complicated and very specific structure. I'll give you a little bit of an understanding of the architecture of the mucus itself when we get to the next slide, because there's a difference between the large and the small intestine mucus for very, very deliberate and important reasons.

But the mucus layer is a really important area to slow down the progression of things that are moving through the lining of the gut, through the entire mucosa, and it also provides a stopgap, to stop things from directly interacting with your intestinal epithelial cells or the immune cells in the intestinal epithelium. So remember, the epithelium is referring to the
lining of cells, the intestinal cells that line the barrier, and within that lining of the epithelial cells, there's a number of different categories of cells. You've got epithelial cells, which are just barrier cells, so just think of them as soldiers blocking the way, standing shoulder to shoulder. But every few cells, you've got immune cells. So you've got L cells, M cells, Paneth cells. These immune cells are incredibly important, because this is the largest area of sampling and immune development in your body.

So you've got lots of immune cells throughout that line of barrier cells that are constantly sampling, and having conversations with your microbiome, and trying to understand the foods, and the antigens, and the toxins and all that are coming into the system, so it prepares your system to deal with all of that. So you've got immune cells, you've got barrier cells, and then you've got neuroendocrine cells. So these are neurological cells that have both neurological and endocrine function. So they can create neurotransmitters, they can create hormones, they can create lots of different things to get your body to be able to respond to what's coming in.

Remember, your digestive tract is the largest exposure of things trying to enter into your body. So you're eating, you're drinking, and you're breathing things in, you're getting exposed to all the air. All of that stuff is going into your digestive tract, one way or the other. And as a result of that, you have to have these really important classes of cells that help your body understand what's coming through, and then help your body respond to your environment. That gives us our adaptability. We talked about the immune system in the gut, and that's the most robust part of your immune system, and there's a number of players in that mucus or mucosal immune system.

Number one, one of the most prominent players as part of the immune defense system

is secretory IgA. Secretory IgA, you find it in other secretory fluids as well, like in your teardrops, in your saliva, but it's very abundant in your mucus layer, in that mucin layer. It's secreted by your intestinal epithelial cells, your barrier cells, and the immune cells within the barrier into that mucosal layer. And it acts as a very, very important part of the defense system. It does a number of things. Number one, is the way your body designs this IgA, this antibody is it has a lot of affinity for a lot of different types of molecules.

If you recall, immunoglobulins or antibodies are very specific to specific antigens, right? So remember, if you have IgG, for example, you have B cells in your immune system that are producing IgG antibodies, that's your long-term immunoprotective antibodies, to say a flu virus that you got exposed to 10 years ago, you still have that B cell in your immune system, ready to produce that one antibody in case you encounter that flu cell again. That's what gives us immune protection. That's adaptive immunity that allows us to get sick from something, our body learns what that thing is, it produces protection against that thing through IgG antibodies that is very specific for that one thing. And then, that cell that makes those antibodies are always sitting and waiting until you see that one thing again.

When you encounter that one thing again, that cell goes into action through a complex immune cascade, and then it produces a bunch of that antibody, but that antibody is highly specific to that one antigen, right? If you've got influenza, H1N1 exposure four or five years ago, you've got H1N1 antibodies in your system waiting for the next time you encounter it, but those antibodies don't bind anything else. They're very, very specific for the H1N1, based on structural elements of that virus. IgA is designed differently. IgA has a multiplicity of capability of binding things. Those antibodies can bind mold toxins, they can bind bacterial components, they can bind viral components, and there's a significant amount of intelligence that goes into how your body designs the IgA antibody, so it has this real broad facet in binding lots of things that could be dangerous.

It also binds lots of things that are benign. So it binds a lot of food particles, it binds a lot of commensal bacteria, so that it teaches your immune system not to have to attack those things when your immune system sees it. When your immune system sees something that's bound by secretory IgA, it refrains from attacking it, right? That's part of how you end up getting tolerance, because you don't want your immune system targeting your own commensal bacteria, you don't want your immune system targeting food particles and things that you should be tolerant. And also, if IgA has neutralized something that's potentially dangerous, like a toxin or like a potentially pathogenic bacteria or virus, you don't need your immune system upregulating, creating inflammation. It's already neutralized, right?

So if something has been bound by IgA, in the mucus layer, in your saliva, in your tears, in your secretory fluids, it doesn't elicit an immune response, and that's exactly what you want. But in order for that to work properly, you need a lot of IgA, and you need very diverse IgA structures, so it can bind lots of different things. The diversity and the expression of IgA is dependent on the microbiome, right? So the microbiome activates certain immune cells through crosstalk from that mucus layer. It activates immune cells to start to express something called pattern recognition receptors. Pattern recognition receptors can read patterns on lots of different things, on different viruses, different bacteria, including our commensal bacteria, food particles, different types of antigens.

And as a result of reading all those different structural patterns, it produces a huge variety of IgA, and then it secretes that IgA into the mucosa. So that is a service that the microbiome is providing to the immune cells, saying, "Hey, I'm going to show you all these patterns. I'm going to help you upregulate your pattern recognition, and then I'm going to stimulate you to produce more IgA, so that all the things that are coming into the system that can be neutralized by IgA won't elicit an immunological response." That's a very important part of our system, that is called oral tolerance. The first step in losing oral tolerance and developing things like sensitivities to foods, vulnerabilities to

infection in the gut, vulnerabilities to shifting microbiome, like the development of SIBO and so on, is this lack of IgA diversity and lack of IgA concentration.

Because if IgA is not neutralizing something that's present in the mucosa, it's going to elicit an immune response, and always remember that the first line of defense in your immune response is an inflammatory response. That's the innate immune system. So if you don't have adequate IgA in your mucin layer that's neutralizing things, those things are going to elicit an immune response. The immune response is going to be an inflammatory immune response. That inflammatory immune response can damage the cells and the structural elements around it, and you start to lose tolerance. So that's in a very important cycle, and it's really important to understand what IgA does, right? It's not only protecting us by neutralizing potentially harmful things, but it's also preventing your immune system from reacting to things it shouldn't be reacting. So keep that in mind.

Now, here's the other thing. When your body doesn't have adequate levels of IgA, if you're not getting stimulus from a healthy, diverse microbiome to produce enough IgA, your body understands that you need some sort of immunoglobulin in your secretory fluids, because that's an important first line of defense. So as a result of not getting enough stimulus to produce IgA, your body upregulates cells called eosinophils and basophils to produce IgE, so that's a different kind of antibody. The problem with IgE is when it binds something, it actually activates hypersensitivity cells, like eosinophils and basophils, that then release things like histamine and leukotrienes that cause an allergic-like response.

So your body's backup for not having enough IgA is to upregulate IgE, but IgE doesn't solve the problem at all, because not only does it not bind as many things as IgA can, but when it does bind something, including a food particle that is just benign, it doesn't need to be afraid of it, but when it binds that food particle, it upregulates a histamine-leukotriene response, and can even activate mast cells and so on. So just having dysfunctional IgA alone, not having enough, not having diverse IgA can create

a mass amount of immunological issues that spiral out of control into food intolerances, allergies, asthma, low diversity, that then leads to leakiness in the gut, because of the constant inflammatory damage in the lining of the gut or the inflammatory attack in the lining of the gut, hormone imbalances, metabolic syndrome, everything can cascade from there. So it's really, really important to note that IgA is really important to have an adequate amount.

Defensins, these are antimicrobial peptides that are released by the intestinal epithelial cells and the immune cells within the mucosa, and these are, again, stimulated by the microbiome, and stimulated in the small intestine by bile, by the presence of bile. And so your intestinal epithelial cells and all that are constantly secreting antimicrobials into that mucous layer, to keep the microbe growth under control, and to potentially ward off any pathogens from establishing itself. The intestinal alkaline phosphatase, which is an enzyme in that, not the musical layer, but the mucosal layer, that detoxifies harmful substances like LPS, and maintains a healthy microbiome, and tight junctions, and all that. So think of it as like a detoxification, buffering, neutralizing agent that's really, really important, again, released by the intestinal epithelial cells, more often than not in response to the presence of a diverse microbiome that stimulates the release of this.

And, then the GALT, the gut-associated lymphoid tissue is part of that mucosal immune system as well, and contains upwards of 70% of the body's immune cells. So think about immune cells throughout your entire body, 70 plus percent are in this gut associated lymphoid tissue, and this is where a lot of the sampling is constantly being done. Your immune cells, in cooperation with the microbiome, are sampling things that are coming through, and then with the right context of the microbiome, is producing IgA against many of those things, or developing a form of tolerance against many of those things, by being regulated by something called regulatory T cells, right? Regulatory T cells are the second way of defending against unwanted immune responses.

The first way is having high diversity and volume of IgA. The second thing is the

presence of regulatory T cells. These are T cells that are monitoring all the immunological responses in the body, and when it sees an immunological response that shouldn't be happening, it can stop and dampen that response. It can reduce, for example, your immune system attacking

ragweed, or pollen, or protein from food. It can stop that, or your own cells, so it can stop autoimmune responses as well, and then it can teach those immune cells that you don't have to respond to that next time. That is another part of immune tolerance and adaptability. The thing is, the upregulation of the T regulatory cells are also dependent on the presence of a diverse microbiome, right? So IgA and the T regulatory cells need a diverse, healthy microbiome, in order to be expressed and function properly.

This is why, when you don't have a diverse microbiome and you have higher loads of pathogens and lower loads of keystone species, you start to see these immunological issues start to creep up. And we're seeing that of course now at an earlier and earlier age, when you think about things like allergies and asthma, which are epidemics in childhood right now. And then even adults who were tolerant of certain foods and things earlier in life, now become intolerant of those foods, and later on in life, that's a clear example of the loss of tolerance, which means one of those two, if not both of those immune system functions are not functioning in the right way. If you used to be able to handle this kind of food, like let's say you used to be able to handle nightshades, and then all of a sudden now, nightshades are very inflammatory and cause problems for you, that means that there's a loss of oral tolerance.

It's an immunological dysfunction that stems from a change in the microbiome. It's not about the food. It's not that nightshades are bad, it's not that lectins are bad, it's not that these other components of fiber is bad, either soluble or insoluble fiber proteins are bad, right? It's not about meat being bad, saturated fat being bad. It's your system is not tolerating it properly, because it's lost some of these functional mechanisms, right? And that's where I see a lot of things with diet, and diet is a difficult one, because

people get very activist about their diet positions and so on. But at the end of the day, outside of processed and ultra-processed foods, and we'll talk about some of those things, real foods that we're talking about, there's very few that are genuinely bad for you, and those foods often that people get a bad response from, it's as a result of their system being dysfunctional, not the food itself being kind of a negative thing.

This is where dendritic cells, mast cells, and all that come into play as well. When you have a dysfunctional immune response, you can get an over-expression of mast cells, dendritic cells in your mucosa. But generally, mast cells and dendritic cells are supposed to be there, because they're monitoring the barrier, and they're trying to look for things that are coming through that shouldn't be coming through, and then they will attack them when they do. This is supposed to be happening in a very light level in this 4,000 square feet of surface area. You're supposed to have dendritic cells and mast cells kind of monitoring, and sometimes things may leak through, because an epithelial cell, one of those barrier cells may get damaged for some reason, and then get kicked out. So there might be a temporary gap there. So some things might leak through dendritic cells. Mast cells go there and so some things might leak through dendritic cells. Mast cells go there and stop the potential toxicity of things leaking through until that intestinal epithelial cell can be replaced. But if this is happening throughout 100 square feet of that space, at 200 square feet or a thousand square feet of that space, it becomes overwhelming for the system.

Lesson 2: An Introduction to Intestinal Physiology

So let me get into a little bit more of the structure, right? So now you see that there's a difference between the small intestinal structure and the large intestinal structure. The real important thing, and you don't see it in this illustration, I'll show you in the next one, is the level of mucus on here, right? So I'll focus on that in the next slide because I have an illustration for that. But the important thing here to see in the small intestine is

remember that the small intestine is about 20 feet long.

From a circumference standpoint, it's much smaller than the large intestine, but the surface area is massive because of these villi structure, right? So the villi structure is structured that way, these finger-like projections are structured that way to dramatically increase the surface area of the small intestine. And it increases the surface area, but in order to increase the absorption of nutrients throughout the surface, right? Your body wants to be able to assimilate and absorb nutrients as quickly as possible. So remember I said the mucosa is a number of structures in one. So you see here this is the mucosa, which is the intestinal epithelial cells themselves. So these are the cells here. The mucosa, it's on top of the cells, and then this inner layer, this is called the lamina propria or the basolateral circulation. So when things go past, the intestinal epithelial cells are in this yellow area right here. They're officially inside the body now, right?

And then here's the muscularis. This is that layer of muscle that is the smooth muscle cells that control the contractile motion of the intestines. And then beyond that, this is the submucosa, now you're passing the intestinal lining itself. And then down here's the muscularis is also another layer of muscle and then a deeper layer of muscle and intestinal cells as well. But as you can see, once something enters into this yellow space right here, it's already exposed to circulation. You see all of these vessels and veins and lymphatics and all that that are in there, all of those, those capillaries and all that now are exposed to any sort of toxin or anything that goes through the single cell layer thick of intestinal epithelium, right? And it's already officially inside your body at that point. A lot of it ends up going into the intestines, but within the cells, within the intestinal epithelium, the cells, you see absorptive cells.

So these are the barrier cells of the intestinal epithelium. Things can either move through the cell, which is the transcellular pathway or between the cells, in the tight junctions, which is a paracellular pathway, right? Then you have goblet cells, these are cells that make the mucus layer. You've got the entroendocrine cells that I

mentioned, and then you've got paneth cells and other immune cells within this layer as well. Now as you can see, a big difference here with the large intestine is you don't have the finger-like projections the same way. Instead, you have these depths, these called crypts, so it dips down. You don't need as much surface area in the large intestine. It already has a good surface area from the circumference of the large intestine, but you don't need these finger like projections, right? But on top of this red area here is where you see the mucus sitting, right, and in the intestines you got the mucus that's following all throughout these finger like projections, right?

So hopefully that makes sense, that the physiological structures are different. The finger like projections are really important to note because it provides a lot of surface area and a lot of area for things to go wrong. The mucus layer in the small intestine, as you'll see... Oh, one more thing on the villi, you've got microvilli, right? So not only do you have millions and millions of these finger-like projections as you see here, right? On top of each of the epithelial cells, you've got even smaller finger-like projections called microvilli. And at the very border of that microvilli is where the mucus is secreted out and the mucus adheres to this top layer of microvilli, right? So imagine on top of this microvilli, you get mucus being built up like that. The mucus in the small intestine is actually a different types of structure than the large intestine. I'll show you in the next slide.

But the villi create surface area, the microvilli create even more surface area, and right at the surface of the microvilli, you have brush border enzymes. So these are enzymes that are sitting there to further break down food and all that to help absorb it through these absorptive cells. Or you have enzymes that can break down potential toxins and issues. So here's the mucus. So you see the difference in the mucus, right? So this is the mucus layer of the small intestine. It's a relatively thin layer, but it's all over the microvilli, right? And it's in between the microvilli as well. And the microbes can live all throughout this mucus layer here, and the mucus layer is there to slow down the transmission of food particles and anything else that's trying to be absorbed into the

system. And this is the lumen side. This is the opening of the intestines. This is where the food and all enters in.

It enters in this way, and then it makes its way through the mucus and then the mucus slows it down. The microbes in the mucus do some decision making and communicate with the immune cells that you see here in blue, right? And then it transmits information back and forth to the immune cells to tell the immune cells what's coming through. The immune cells then secrete things like antimicrobials, IgA, all defensins to protect these intestinal epithelium. And then food particles even that are making it through gets slowed down by the presence of the intestinal epithelium, sorry, the mucus layer here. Now in the large intestine, so in the colon you see here, there's two distinct layers of the mucus. You've got this top layer here, the outer mucosal layer, which is a thinner layer, which is where all the microbes live. And then you've got this impenetrable inner layer. This inner layer is a much thicker gel-like structure. It's called mucin 2, and there's no microbes that live here.

In fact, it's the only sterile part of your body. Almost everywhere else in your body, you've got microbes even in your blood, even in your cerebral spinal fluid, even in your brain. But this area which is just adjacent to the highest concentration of microbes in the body. So this area of your body has something like 25 trillion, 30 trillion microbes, and the area just adjacent to it is the only sterile region in your body, right? That geographic separation is really important for the immune cells that line your intestinal epithelium to make those immune cells comfortable that you're not getting a massive flood of microbes trying to penetrate through that final cell barrier. That geographic separation is really important and that has to be maintained in order for the large bowel to function the way it should, the immune cells in the large bowel to be happy, and then the microbiome within the large bowel to also function the way it should, right?

So hopefully this makes sense in the difference between the small bowel and the large

bowel, the mucosal structure, the barrier structure, the mucus in itself, how it's structured, how it functions, and where all the microbes live, right? So remember in the large bowel, the microbes live in this outer layer of the mucus, in the small bowel, the microbes live everywhere throughout the mucus, and then in the large bowel you've got the sterile region of mucus as well. And you don't have the finger-like projections, you in fact have these crips that are shown by inverted finger-like projections down, right? So we don't need as much absorptive surface area in the large bowel. We need as much as we can get in the small bowel. Now, when you start to look at small bowel diseases, so for example, celiacs or people that have suffered with a lot of inflammation in the small bowel, people with severe leaky gut or enteropathy, which is this way of defining a devastation of the small bowel structural elements, what you start to get is these microvilli start to shrink, right? They become shorter and shorter and shorter.

When you start to see these microvilli shrinking, for example, we go back here, you see these finger-like projections. If they start to shrink down and become smaller and smaller, let's say they were a millimeter tall, and then they become 0.5 millimeters, 0.3 millimeters, that is something called enteropathy. Enteropathy means that there's a dying of the tissue, the enteric tissue, right? And that's one of the consequences of having constant inflammation in the small bowel. This is seen in celiac disease because they react violently to the presence of gluten. This is seen in infections like HIV for example, because HIV, the virus initially infects gut cells quite a bit, activates something called CD-8 positive T cells because it's killing the CD-4 T cells. The CD-4 T cells are the adaptive T cells, the CD-8 T cells are the very inflammatory T cells. And so because it's constantly activating CD-8 T cells in this small gut area, it's causing a lot of inflammatory damage to the small gut.

So you start to see a shrinking of the microvilli. What happens when you shrink the microvilli? Well, you also lose surface area, right? And if you lose surface area, you're

losing the absorptive capability of the small intestine. The other thing that goes wrong with the small intestine is you lose this mucus layer or parts of it, and then you start damaging these intestinal epithelial cells and you start to find big gaps where those cells have not been replaced fast enough, right? So leaky gut in the small intestine tends to look like a damage to the mucus layer, which is already thin to begin with, and then damage to the tight junctions in between the cells, and then actual damage to the cells themselves, where the cells themselves are kicked out because they're damaged and haven't been filled by a new cell.

To fill that space with a new cell, you need the right microbes in the microbiome to elicit an interleukin response. So the microbes in the microbiome manage all of these structural elements, right? So if a cell gets kicked out because it's damaged, the microbiome elicits an immune signal that activates genes to get a replacement cell in that spot. And also, the production of mucus also requires things like short chain fatty acids and other activation by the microbiome. The expression of the type junction proteins, the proteins in between the cells that can open up the cells and close up the cells and for the tight junction proteins becomes damaged, the cells stay open. Permanently, those proteins also require the expression of the microbiome, and then of course, the function of the immune system itself in order to be tolerant of all the things that are coming through the small bowel needs the microbiome, as I mentioned, because of the secretory IgA component and the regulatory T cells, right?

So all of the structural elements within the small bowel that makes it a dynamic barrier, the mucus, the tight junctions, the immune cells, the defensins, IgA, the regulatory T cells, all of those things require the function of the microbiome to keep them up and upregulate them. Same thing in the large bowel. The production of this mucin 2 layer, this sterile layer, which is very important, the tight junctions, again, the replacement of damaged epithelial cells, the production of that top layer of mucin, the production of antimicrobials to defend against dysfunctional bacteria that may actually set up in that mucin layer, all of those things require the microbiome. So all of the structural elements

and the functional elements of the barrier system require a functional microbiome and a diverse microbiome with lots of keystone species in order for them to act the way they're supposed to act, right?

So you can easily see, as the microbiome starts to dismantle and starts to shift losing diversity, losing keystone species and protective species, increasing the presence of pathogens that aren't helping these structural elements, you start to see how easily the structural elements start to become dysfunctional. And given you have 4,000 square feet of this area, it's not hard to see how certain areas can start to become dismantled and propagate more and more dismantling throughout the system, right? So the epithelial cells and tight junction, again, the epithelial cells is that physical barrier that marks the last vestige of a separation between outside the body and inside the body. When something goes through this final epithelial cell and ends up down here in what we call the basolateral circulation, it's officially inside the body now. The tight junctions are the spaces in between. There are 40 or so proteins in between each of these cells called claudin and occludin proteins. They're like shoelace-like proteins. They cinch the cells, the cells shut, and then sometimes they allow them to open up to allow certain things through, but normally they're supposed to be cinched shut.

These proteins and the expression of the proteins are dependent on the microbiome, but you have to have those proteins functioning to keep this barrier system functioning properly. Zonulin is one of those proteins that regulates the opening and closing. This is why they've used zonulin in certain research trials to try to gain an association between elevated zonulin levels and potential indication of leaky gut. And it's not a direct diagnostic yet, zonulin is still correlative to that, at least the way you read it in your stool samples. But keep in mind that that's where zonulin functions. It functions as a regulator of the opening and closing of the tight junctions. And when the mucosal barrier and tight junctions are compromised, it leads to this immune chaos creating inflammatory responses, right? And keep in mind that the mucosal barrier and the tight

junctions become compromised because of a dysfunctional microbiome to begin with. And because that dysfunctional microbiome is also not helping the secretory IgA and the Treg cells, your immune system's going to be going haywire in that junction to begin with, right? So all of this becomes a self perpetuating cycle.

Lesson 3: The Consequences of Leaky Gut

So what's the consequences then of leaky gut? It's all of these conditions, right? I talked about it in an earlier webinar, but all of these conditions, sensitivity, skin conditions, brain fog, metabolic disorders, pain, autoimmune, of course, respiratory issues, immune dysregulations, all of these things are a result of leaky gut. Now, how can all of these things that are seemingly unrelated to the gut be a consequence of leaky gut, right? I'll show you that in an upcoming slide, but just keep in mind, all of these things that aren't gut-specific are a consequence of leaky gut. And the big consequence, and this is the real molecular connection between how all of these disease states can stem from leakiness in the gut, is this concept of endotoxemia, right? Metabolic endotoxemia is when you have a disrupted barrier system. So disrupted mucosa, tight junctions, messed up intestinal epithelium, low diversity in the gut, microbiome that drove all of those things, low keystone species, overgrowth of pathogens and so on, and especially the elevation of gram-negative bacteria. I'll talk about what that is in a second. All of those features lead to this concept of endotoxemia.

Endotoxemia is often called metabolic or postprandial endotoxemia because the biggest spike you see in toxins in your circulation is after a meal. Four to five hours after a meal, you see the highest peak of endotoxins in circulation when your gut is leaky. This is why this has become a very definitive way to measure leaky gut in an individual, right, is you're looking for postprandial or metabolic endotoxemia. If your gut is leaky and damaged, you eat a meal, four hours after that meal, you see a huge influx

of LPS in systemic circulation, right? If your gut is not leaky, you can eat that same meal, four hours, five hours after the meal, you barely see any bump up in the amount of endotoxins. That is the definition of endotoxemia, which is the consequence of leaky gut. So it's a great way of actually measuring leaky gut.

Now, the endotoxemia leads to this pathology of chronic low-grade inflammation, right, and chronic low-grade inflammation can start the cascade of things like insulin resistance, elevated blood sugar levels, type 2 diabetes, obesity, weight gain, increased visceral fat, cardiovascular disease, so everything under the cardiometabolic banner. All of those disease states, which are the top four killers in the western world. All of those things, which also then become independent risk factors for other chronic conditions, right? All of those things come as a result of endotoxemia, right? Endotoxemia is often in the literature described as the primary insult to some of these. I'll show you a couple of those papers. Normally when I'm lecturing to doctors and clinicians, I go through a lot of that research. There's just tons and tons of meta-analysis and papers on this, but I'll show you a couple just so you get a sense that the research is showing this as well. But keep in mind that metabolic syndrome in the western world is one of the biggest underlying chronic disease states that people face.

And a lot of other diseases, so cancers, immune dysregulations, neurological things like Alzheimer's, Parkinson's, dementia, all of those things come with significant increased risk if you have metabolic syndrome. Even something like COVID, for example. Here comes a virus that our system has never seen before. A 50-year-old with type 2 diabetes had 10 times higher risk of dying from being exposed to COVID compared to a 50-year-old without type 2 diabetes. Ten times, right, that is a huge difference in how one individual can handle something like a new virus versus another individual that handles this new virus. What is the difference between the two? It's not the diabetes, it's not the blood sugar resolution or incorrect resolution of blood sugar. It is the endotoxemia that that individual had that led to type 2 diabetes, and they still have

elevated endotoxemia, right? Diabetics, obese individuals, people with cardiovascular disease, people with some degree of insulin resistance, and even pre-diabetes all have significantly elevated endotoxemia and significantly elevated leaky gut. And it's the leaky gut that came first in all of these cases, right?

That's what the meta-analysis studies have shown. They've even published by the American Diabetic Association, and most of these large research institutional bodies are way behind often, but they've been ahead on this particular science, right? So keep in mind that metabolic endotoxemia is the consequence of a leaky gut. Leaky gut is a consequence of microbiome dysbiosis, and at the end of the day, metabolic endotoxemia leads to things like chronic low-grade inflammation, and then the development of metabolic syndrome in individuals, right? So then you get cognitive dysfunction, brain disorders, liver dysfunction, non-alcoholic fatty liver disease, fibrosis, and cirrhosis of the liver are also now very much tied to elevated levels of endotoxemia in individuals, right? So the gut is no longer protecting the liver. And on top of that, the gut is extremely toxic to the liver so the liver is undergoing a lot more damage than it normally should, hormone imbalances, autoimmune disease, and so on.

Metabolic endotoxemia at the low end is approximated to impact around 50% of the adult population. We've seen a little bit higher in some of the clinical trials that we've done, but at least 50% of the population is affected by it, right?

Lesson 4: Understanding Metabolic Endotoxemia

When you look at endotoxemia, what is this LPS thing? We talk about lipopolysaccharide, which is the endotoxin that's being absorbed through the lining of the gut in a leaky gut and ending up in circulation, right? So what is this LPS? Well, it's an inflammatory immunogen, meaning it's a component of a type of bacteria called gram-negative bacteria.

So every bacteria in the world that's ever been discovered can be categorized as gram negative or gram-positive. The main difference between the two is gram-positive bacteria have a cell wall structure, so they have an inner membrane, and then they have a cell wall, which is much more of a rigid wall. Gram-negative bacteria don't have the cell wall. They only have a cell membrane, and within that membrane, they have these LPS components. Now, the bacteria use them for lots of things, for communication, for binding, for things that bacteria need to do. They're not particularly harmful when they're in the whole bacteria. But when LPS is released because a bacteria lysis or dies in the gut

When LPS is released because of a bacterial lysis or dies in the gut, you end up with that LPS being free on its own and eliciting an inflammatory response because it is an inflammatory immunogen. Your immune system is designed by nature to look for LPS because it indicates the presence of gram-negative bacteria, and lots of gram-negative bacteria are pathogens or opportunistic pathogens. In fact, when someone dies from sepsis or septicemia, it's often because they got too many gram-negative bacteria in circulation. So gram-negative bacteria that contain this LPS is something that your immune system is always watching out for to try to protect you from sepsis. And so when it sees LPS, even if it's floating on its own, it elicits a really massive immune response. And so the LPS is very abundant in gram-negative bacteria. Keep in mind that a single gram-negative bacteria can have between a million and 10 million LPS molecules in its membrane.

And about 50% of your microbiome are gram-negative bacteria. Something like 80% of the microbiome in your mouth are gram-negative. So imagine if in your gut where you've got somewhere around 30 trillion organisms, half of them, 20 trillion or so are gram-negative. Let's say at any given time when you're eating food. And this is why metabolic endotoxin or postprandial endotoxin is labeled that way is because the process of eating and digesting food kills a lot of microbes, especially in the small bowel because you're releasing acid from the stomach that's entering into the small

bowel. We talked about how all that happens a module ago, release of pancreatic enzymes which also kill bacteria. The specific release of antimicrobial peptides and bacteriocins from the intestinal epithelium to try to control bacterial overgrowth in the small intestine, that kills a lot of bacteria. The release of bile. Bile is an antimicrobial. It kills a lot of bacteria. And just the churning and the action of food digestion in the small bowel kills a lot of bacteria.

So during the digestion process, lots of bacteria is going to die. So if you've got say, 20 trillion, 30 trillion bacteria in your small bowel... Or you probably wouldn't have that much because a small bowel has a smaller concentration. Let's say you have a trillion bacteria in the small bowel and 20% of them die. So you've got two, 300 million bacteria that die during the digestive process. Half of them are gram-negative. So you've got about 100 trillion bacteria that are gram-negative dying in a meal, and each of those 100 trillion bacteria are releasing one to 10 million LPS molecules. The number of LPS molecules that are being released during digestion is mind-boggling. And if your gut is leaky, a huge percentage of that LPS is leaking through and entering into circulation. Instead of being sequestered and caught by the IgA and the mucus in the small bowel and not being allowed to leak through.

So this LPS is very abundant in the gut. It leaks through when your gut is leaky and you have too many gram-negative bacteria and a combination of both of those things. And when it leaks through and it's circulating on its own, your immune system sees it as a direct threat and expresses a very profound immune response wherever it sees it. In fact, it's so profound that your immune system actually secretes a protein called LBP, LPS binding protein that constantly circulates through your body looking for LPS. And when LBP sees LPS, it grabs onto it and it takes it to the dendritic cell or macrophage, and it shows a dendritic cell and macrophage that, hey, there's LPS around here. We really need to up regulate the immune response because it thinks that there's pathogens in the area. And the part of the LPS that elicits all of the immune response and toxicity is this lipid A-tail.

Now, you'll see through the presentation that saturated fat, certainly a high-fat diet and saturated fat specifically can increase endotoxemia in people with leaky gut. That always becomes a controversial statement because again, people are very activists about their diet. And so if you are a carnivore person or a paleo person, or you are a keto person, they tend to get offended, if you will, by that kind of thinking because they go, well, no, paleo and keto and all that are healthy for you. So how can they elicit more of an inflammatory response? The fact of the matter is if your gut is leaky, it can't protect you against endotoxemia the way a normal gut is, and a normal healthy gut can eat any of those things without them causing a problem. But if your gut is leaky, what tends to happen is an elevation in saturated fat and fat in your diet alone can increase endotoxemia and the immunological response of endotoxemia for a couple of reasons.

So number one, you look at this endotoxin, the top part here is a polysaccharide, meaning it's a sugar, it's like a carbohydrate, if you will. But the bottom part and the largest component of the endotoxin structure are these lipid tails. So to your body, LPS kind of looks like a fatty acid. It has these lipid tails to it, so it looks like a fatty acid. So one of the ways in which your body absorbs dietary fat, which is really important to absorb, is that the intestinal epithelial will secrete lipid rafts. These are carriers that go out and grab dietary lipids and bring it through. Or dietary lipids are brought through on immune cells or these other carriers called chylomicrons. These are like little encapsulators that grab dietary lipids and bring it inside the epithelial cells. Inside the epithelial cells, they are converted to lipoproteins.

This is where LDL comes from and HDL comes from. LDL is low density lipoprotein, HDL is high density lipoprotein. These are examples of lipoprotein carriers that are made in the body in the lining of the cell and liver to some degree. And triglycerides is another carrier system to take fats throughout the body from the intestinal lining and from the liver, and carry those fats throughout the body where it needs to go. Well, why is it doing that? Because remember, we covered this in module two, I think, where fats don't solubilize in the body because the body is generally an aqueous environment.

Fats and water don't mix, but the cells are aqueous. Your circulatory system, your blood system, your lymphatic system, they're all aqueous. So fats don't mix or dissolve in those aqueous solutions. So bile helps with creating the surfactant. Remember, the role of bile is to create the surfactant around the fat that's in the digestive tract.

The surfactant fat now moves into the cell. In the cell, they put it into carriers like chylomicrons, low-density lipoprotein, high-density lipoprotein, and it gets carried throughout the body. This can happen to LPS as well. So LPS can get surfactant by the surfactant action of bile. It can grab the LPS, pull it into the cell, the cell can put chylomicrons around it and carry it throughout the body. So it's carrying a toxin throughout the body inadvertently. And your body makes more and more of this when you eat more and more fat in your diet. So imagine you've got a trillion LPS being released in your gut during digestion, and you've got a whole bunch of fat in the diet. Your body's going to ramp up the activity of bile and chylomicrons and carrier lipids in order to grab the dietary fat and use it.

So as the process of ramping the ability to grab the dietary fat, it's going to grab more of that trillion LPS. Versus if there's a lot of fiber and protein and other things coming through, it doesn't upregulate the fat absorption as much so it doesn't inadvertently bring in as much LPS. So that's one reason why higher fat intake will increase more endotoxemia. The second part of it is saturated fat has very similar structural elements to LPS, to the lipid A component of LPS. So saturated fat can elicit an immune response itself, especially if you don't have high tolerance in your microbiome and immune system. So if your immune system is dysfunctional, if you've lost tolerance, if you're sensitive to lots of foods, if you have leaky gut, then saturated fat can increase immunological response in the lining of the gut and in circulation as well, because it has very similar structural elements to this lipid A tail that your immune system is always primed to look for. So hopefully that makes sense.

Now, it doesn't mean that meat or saturated fat is inherently bad. What it does mean is that if you have leaky gut or you suspect you have leaky gut, then you probably should

not go on a strict carnivore diet or paleo or paleo in the sense that it's highly ketogenic and so on. And maybe there's times to be able to do that and do that with a practitioner, do it for a short amount of time and so on. But it doesn't mean the food is bad. It means your system is not handling the food properly. If your system is perfectly fine and healthy, you can handle all the fat and you can handle all the saturated fat and get all the benefits from the meat. And meat can be very healthy for you. But if your system is not functional, you won't be able to handle it as well and it could perpetuate even more problem. So hopefully that makes sense to individuals.

So this just gives you a little bit of an illustration of all the different things that can happen as a result of a dysfunctional diet that drives endotoxemia, that drives immune response, that drives microbiome dysfunction and so on. So just a couple of things to mention here. So when you look at, let's just take this as an example of poor dietary choices. Heavily processed foods with lots of pesticides, herbicides, antimicrobials, poor quality nutrients, high sugar levels, all kinds of things that we know are bad for you. One of the consequences is of course, increase endotoxemia by increasing lipopolysaccharides. And that endotoxemia drives a lot of inflammation and a lot of dysbiosis in the system. It also increases this hypoglycemic and high fat response as a result of eating this type of food. This can also increase inflammasomes and inflammatory molecules in the gut.

And then systemically, it also elevates histidine and the issues related to immunological function in the gut microbiome. You also have this issue of central adiposity. You get macrophages infiltrating fat cells. You get the fat cells producing lots of hormones that are really bad for your system, for your metabolic system, releasing pro-inflammatory cytokines. The macrophages up-regulate immunological responses within the fatty acid tissue, and you get this central adiposity issue. And then ultimately, most of these things lead to a disruption in the gut microbiome and a barrier dysfunction and immune dysfunction. So ultimately, all of these pathways lead to a further disruption of the gut

microbiome, further activation of the immune system in an unfavorable way, further permeability issues, so more leakiness, more inflammation. And then ultimately you end up with all of this metabolic syndrome. And metabolic syndrome is the most common form of underlying chronic disease in the western world.

And then most other risks of chronic disease stem from metabolic syndrome. Of course, you can develop other chronic diseases without the presence of metabolic syndrome. But we're speaking in generalities here and generalities, metabolic syndrome is an underlying factor for most chronic disease. Just to show you a couple of examples here, so this is a study called the Cordeoprebs Study. They followed 462 patients over, I think it was a 60- month period who had high risk for type two diabetes in general, not necessarily early onset. But they were looking at people who had a high risk of developing type two diabetes, meaning they were probably pre-diabetic or they had other core morbidities like overweight and other issues that would likely lead them to developing type two diabetes.

They followed these individuals and they looked at all of the biomarkers involved in their system. And they were trying to find a biomarker that was predictive of the development of type two diabetes from being high risk to develop type two diabetes. They showed that postprandial endotoxemia was the best predictor of developing type two diabetes and precedes the development of type two diabetes. Meaning an elevation in postprandial endotoxemia came first. And then the presence of LPS was not only a driver of the formation of the resulting type two diabetes, but also could be used as a biomarker predictor of the development of type two diabetes. And keep in mind, type two diabetes is the biggest health crisis we are facing today. When somebody is diagnosed with type two diabetes or they're at that level with their A1C blood sugar and so on, their risk for every other chronic disease goes up tremendously.

When you have type two diabetes, your risk for cardiovascular disease is two and a half to three-fold higher. Your risk for Alzheimers, Parkinsons and dementia is two and a

half to three times higher. Your risk for autoimmune conditions and cancers and all of that stuff goes way up. Your risk for obesity and all that goes way up. Of course, you have peripheral vascular disease and neuropathies and blindness, and all of these things go way up when you develop type two diabetes. So type two diabetes is a very, very dysfunctional state for the body to be in. And it's one of the biggest risk conditions to have because it drives risk for all other conditions. And endotoxemia is the driver of the formation of type two diabetes. It's arguably one of the most potent drivers and one of the most potent predictors of the development of type two diabetes.

And on the globe today, we already have something like seven or 800 million type two diabetics. But we currently have four times that many pre-diabetics, 80% of which will end up with type two diabetes. So over the next 10 to 15 years, we will see the presence of upwards of four billion people on earth with type two diabetes. Novo Nordisk will become the number one most valuable company in the world. It's up there as number two or three in terms of pharmaceutical companies, because they're the biggest producers of insulin in the world. They're probably in the top 15 most valuable companies in the world. Apple of course, being the most valuable company in the world, I think worth three trillion dollars.

But over the next 10 to 15 years, Novo Nordisk was also the developer of one of the GLP-I ozempics, is going to become one of the most valuable companies in the world.

And the problem with that is those four billion diabetics are going to drive healthcare costs and healthcare management through the roof because of the risk of everything else. Even the risk of fertility issues and low birth rates and hormone imbalances, and everything becomes problematic because of the formation of type two diabetes. And the biggest driver of type two diabetes is endotoxemia and leaky gut, and it's also the biggest predictor. So we cannot underscore how important this issue is. So the first few things I covered in the first few slides, if you really understand that stuff and you really

understand endotoxemia and what happens when you develop endotoxemia. You are wrapping your head around it and understanding the pathway and the biochemistry behind the biggest global health crisis we are currently facing and will be facing in the near future. Then we have cardiovascular disease. We've always known that obesity and type two diabetes increases cardiovascular disease risk.

Well, as it turns out, it was never really understood why? Why being overweight, why having diabetes increases your risk for cardiovascular disease? Now, the studies are showing that metabolic endotoxemia, which is the commonality between cardiovascular disease type two diabetes and obesity, is the molecular connection of why individuals who have elevated endotoxemia, who ended up with type two diabetes and obesity, why they have an increased risk of cardiovascular disease. It's not necessarily the obesity or type two diabetes, it's the underlying endotoxemia that they have in the first place. Remember, endotoxemia precedes obesity, type two diabetes and so on. Meaning it's present at a high level, and as a result of it, you end up with type two diabetes and obesity. And it's that same endotoxemia that also causes cardiovascular disease and every other inflammatory condition in the body. Including things that impact the brain where we now know that microbiome-derived lipopolysaccharides, so LPS can be found in the perinuclear region of the Alzheimer's brain.

And it's a clear connection between what is driving an inflammatory response in the brain that starts to degrade the neuronal tissues. So it is just another connection. And then looking at things like cancer, cachexia. So we know that the wasting syndrome in cancer is one of the biggest drivers of mortality in cancer. And these kinds of big studies are showing that endotoxemia is a key part of the process of the development of colon cancer-related cachexia and other cancers as well. In this particular study, they looked at cancers like melanoma and a couple of other ones, and lung cancer as well. Endotoxemia in these individuals, which was present before the cancer and then gets increased as a result of some of the cancer treatments, is what drives the formation of cachexia which is that wasting syndrome, which is what becomes the

biggest predictor of mortality in cancer in general.

So endotoxemia is really, really potent. Here's a whole bunch of other mechanisms that are driven by endotoxemia. Everything from leptin resistance, chronic constipation, of course, mood, appetite, disruption and then depression, anxiety. In fact, there was a huge Netherlands study called the Netherlands Study on Anxiety and Depression. They found that serum LPS levels was the best predictor of not only the onset of anxiety and depression, but the severity of that anxiety and depression. They can predict it. And this was a nine-year study following individuals. Chronic pain, hypogonadism which is low testosterone in men. In women estrogen dominance is also a feature of endotoxemia, autoimmune issues of course, because of all the immune dismantling that I referenced earlier on. All of these conditions are driven by endotoxemia.

Lesson 5: Root Causes & Drivers of Leaky Gut & Metabolic Endotoxemia

So what is causing all of this leaky gut? I gave you some good insight, I hope, on the structural elements of the small bowel and the large bowel. The elements that prevent leakiness, that allow a dynamic level of judgment of what can move through and what shouldn't move through, and how things are handled in the mucus layer of those organ systems. And a disrupted microbiome is the first step in the development of leaky gut. So anything that disrupts the microbiome in a profound way can be tied to a root cause, driver of leaky gut and eventually metabolic endotoxemia. But let's outline them a little bit. So when we look at diet and lifestyle as contributing factors and root causes, highly processed foods is way up there on the list. And the reason is because highly processed foods have all kinds of components in it that are just not good for the microbiome. Not only do they not feed the microbiome in the proper way, they cause dysbiosis by killing off beneficial microbes in the microbiome.

So we're talking about synthetic coloring agents, flavoring agents, so the synthetic

versions of those especially. We're talking about pesticides, herbicides that tend to be present at high levels, antimicrobials, preservative agents, certain types of emulsifiers. All of these things have a very negative effect on the gut microbiome itself, and those ingredients start to kill bacteria and reduce diversity and create opportunity for the growth of opportunistic pathogens. We also know that food sensitivities and all that occur as a result of this. I talked about that in pretty good detail in the beginning of how that would happen. But this loss of microbial diversity and concentration of beneficial microbes lead to that disruption of secretory IgA diversity and secretion, and then also the Treg cells. Then you end up with food sensitivities and so on. And then of course, unhealthy meal hygiene. We talked about meal hygiene in module two, which is- really.

... Meal hygiene. We talked about meal hygiene in module two, which is really important. So eating too fast, eating on the go, not chewing your food enough, not having enough HCL production, not having enough bile secretion and bile production to help and aid in digestion, and prevent the overgrowth of microbial growth in the small bowel. During digestion, all of those things have an impact on the microbiome, which then has an impact on the physiological structures of the small and the large bowel, and thereby can lead to leakiness in the gut. So I would just pay attention to the types of foods you're eating. Again, you don't have to go on very specific diets and all that, just knock down or cut out if you can highly processed foods or what we are calling today is ultra-processed foods. Some may argue things like a protein shake is a processed food.

It is, technically, because you're taking protein isolates from a normal food, and then often they're adding some flavor to it, a chocolate or vanilla flavor to make it more palatable. And they might add some Stevia or something like that. Yes, it is a processed food, but it's completely different than a Cheerio or burrito, sorry, or Doritos. So there's categories of processed foods, and I know it's really hard for people to just cut out all kinds of processed foods. And then, there are many health foods that are marketed as health foods that are actually processed, but may still be okay. I would

rather somebody eat a what would be a protein bar, which is not fantastic food. It is still processed to a certain degree than let's say Cheetos. So there's still some merit in the protein bar. There's at least some micro and macro nutrient value there versus something in the bag of Cheetos.

But there's a difference between those two versions of processed foods. So try to get yourself back to real foods that's not processed, it's not packaged, it's not manipulated in some way, but just also keep in mind that within the world of processed foods, there's degrees. And you don't have to be hard on yourself to try to eliminate and have a perfectly clean diet, and be very stringent about every last ingredient and every last thing. Just make general movements towards real food.

And then, the meal hygiene, we cover that extensively in module two. Just think about all of those meal hygiene ideas, because those all do matter in terms of how food impacts your system. And then, stress, right? One of the key parts about meal hygiene was not eating when you're stressed and then allowing yourself to calm down, to relax, to find something that just calms you down before sitting down and eating. Or don't eat in the car as you're driving through traffic when you're stressed there, because stress increases dysbiosis and endotoxemia, and it's going to create more problems with the food that you're putting into your system at that point, because you're going to be digesting the food appropriately.

You're going to be eliciting immune responses against that food, because stress and endotoxemia increase inflammation, so you don't want to be eating in that state as well. Alcohol has a negative effect. Of course, if your gut is messed up, your gut is leaky, you're trying to heal yourself. I would refrain from alcohol, right? My goal was always to become resilient, because I wanted to be able to have a drink socially with my friends and not have a massive consequence as a result of it. So I built and worked on my system to try to be resilient, so I can make 15, 20% bad decisions. But if you are in the healing process, it's best to try to stay away as much as you can. Chronic lack of sleep and disruptive circadian rhythm. We've talked about this before,

but having a pattern and cycle to your eating is really important.

And to your rest as well. Sleeping is when your gut lining and lots of other things get repaired. So your gut lining undergoes a lot of stressful things throughout the day, and you're going to have oxidative stress, you're going to have immunological damage, you're going to have cells that are broken and damaged in your lining. You're going to have part of your mucosa broken down. You need to repair all those things. And all of those things only get repaired at night when you're sleeping, resting, you turn on the housekeeping microbes, the housekeeping genes, and you're not putting food in the system, right? That's the only time the lining of the gut can get effectively repaired. So you need adequate rest in order for the repair systems to kick in. So that's really important. And remember, if you have leaky gut, if you have high amounts of saturated fat and trans fat in your diet, it's going to increase endotoxemia.

So reduce the saturated fat. Try to stay away from trans fats in general, because they're very inflammatory, but reduce the saturated fats while you're trying to heal the gut. Then you can go back to eating your regular levels of saturated fats. And then of course, environmental toxins have a huge impact as well, so they can contribute to dysbiosis. So you have to be aware of what toxins are in your region. In fact, there's lots of great resources out there. Laura Adler is a fantastic resource for environmental toxins and how to deal with them.

But there's lots of toxins that you can have in your home, in your region, depending on which geography you're in, you can investigate those things and become aware of those toxins, and then try to mitigate them to some degree. Contributing factors that are associated with dysbiosis and GI environment imbalances. So the elevation of pathogenic organism. So gram-negative bacteria, the ones with LPS, if you recall. Your small bowel is not supposed to have a predominance of gram-negative bacteria. In fact, you should have somewhere around 10% of the bacteria in your small bowel as gram-negative. Most of the bacteria in your small bowel should be gram-positive.

But gram-negative bacteria, are constantly entering into your small bowel. Excuse me. In particular through the oral cavity. So oral hygiene is really, really important to help with leaky gut. You're swallowing hundreds of billions, if not up to a trillion bacteria each day through saliva from your mouth. Of course, there's bacteria coming in through food and everything else as well, but your mouth has something somewhere around 20 to 22% of all the microbes in your body. So it has a huge concentration of microbes, and you're swallowing all those microbes constantly. And a lot of the microbes in your mouth are gram negative, like enterococcus, E. coli and so on. So you need to ensure that oral hygiene is maintained. Fortunately through this course, you've got that other module by, I always pronounce mispronounce his name, but Dr. Birheen is how I'd said it before, but I don't think that's correct.

But Michael will tell you at the end of this how to pronounce his name properly. But he does a fantastic job talking about the oral microbiome and has some great solutions for managing the health of your oral microbiome, and the soft tissue, and the soft tissue palette and so on. But pathogenic organisms is a big source, and the mouth is one of the biggest sources of that. And the absence of beneficial microbes, right? The production of short chain fatty acids is so critical for the maintenance of the entire structure that we reviewed in the first few slides, because remember those goblet cells. Those goblet cells are the ones that produce all that mucus, the small bowel mucus and the large bowel mucus. It produces all the different structures of the mucus. And that mucus layer is so important to protect the gut. The goblet cells feed off of butyrate in order to produce the mucus.

So if you're not producing enough butyrate, you're not activating the goblet cells, you're not feeding them, you're not producing enough mucus. And when you don't produce enough mucus, there goes intestinal permeability issues, right? Mucus is that first line of defense on that entire mucosal structure. So fiber, adequate fiber with the beneficial microbes that convert the fiber to short chain fatty acids is incredibly important to health. I think this is why fiber has been shown to be one of the best longevity foods

there is, right? If you consume fiber in your diet, for every 10 grams of fiber you add to your daily diet, it can reduce your risk of mortality, all cause mortality by almost 11%, right? So it's a huge impact that fiber has. And remember, we don't break down fiber at all and assimilate any nutrients. It all goes to the bowel, the large bowel where it's fermented and short chain fatty acids are produced, right?

So that's why fiber is so important. And then of course, infections and overgrowths in the small bowel, like SIBO, Candida and so on. And SIBO is an overgrowth of gram-negative bacteria in your small bowel. You're allowing gram-negative bacteria. The natural protective mechanisms aren't there to prevent the gram-negative bacteria from settling in. So that kind of increase not only creates massive inflammation in the small bowel, but now you've got too much gram-negative bacteria there with all this LPS that's leaking through. So SIBO is a very profound endotoxic condition, because you've got a dismantled gut lining, you've got lots of inflammation, you've got food intolerances, you've got all the immunological factors, and on top of that, you've got an overgrowth of gram-negative, specifically releasing a million to 10 million LPS molecules per cell. So this is why SIBO is such a big problem, and hopefully we'll be able to tackle that in the modules as well.

And then of course, the absence of beneficial microbes that manage the tight junctions and so on. The microbiome regulates all of the things that we talked about that are protective mechanisms within the mucosa itself, the mucin, the defensins, secretory IGAs, the function of the dendritic cells and so on. It's all managed by the microbiome. And in the absence of adequate, beneficial short-chain fatty acid producing microbes, the gut environment increases in oxygen, increases in the growth of pathogenic organisms, most of them of course being gram-negative, thereby contributing to more leaky gut. Other factors that contribute to leaky gut, the presence of pesticides, heavy metals, herbicides, and other chemicals within the households, within your environment, within your food supply that harm microbes. Alcohol, the overuse of NSAIDs, non-steroidal anti-inflammatories, and many other medications can trigger

dysfunction in the microbiome and thereby an increased permeability in the intestinal lining. Antibiotics, of course, we know that there's lots of antibiotics that are way overused.

There's lots of times when you need an antibiotic, and that's a decision between you and your doctor, but there are at least 50% of the antibiotic scripts are written for reasons that aren't helped by the antibiotic. For example, in viral infections. And of course, antibiotics also heavily used in processed foods and processed meats, and this is why even processed meats is an issue. Now, again, back to this kind of carnivore and plant-based kind of debate. One of the misnomers for those that are in the carnivore sector that are like meat is all healthy, plants are generally all bad. This idea that meat generally is good and they're eating processed meats, right? So if you're buying deli, cuts from the deli that's heavily processed, if you're buying chicken breasts from the deli, that's pretty processed. Most chicken breasts have starch embedded in it. They add starch to the chicken breast under pressure before cooking the breast in order for it to retain moisture and weight when they sell it, right?

So they're impregnating chicken breast with starch. Often it's rice starch, right? So it can be high glycemic in its response. Of course, there's nitrates and preservatives, and all this stuff that are in meat. So processed meat is as bad as any other processed food. So we want to be careful, and they of course use a lot of antibiotics in processed meats as well. We're omnivores. We should eat a balanced diet of real food, not processed versions of anything. And then lack of exposure to microbes, right? We're not getting out enough. We're over sterilizing our environments and things that we've talked about before. And then antimicrobial, personal care products. Soaps, shampoos, mouth washes, over uses of hand sanitizers. All of those things have a huge impact on the microbes as well.

Lesson 6: Reversing Leaky Gut & Reducing Metabolic Endotoxemia

What do we do, right? This is the important part. The microbiome is of course the key.

We've mentioned all of these functions of the microbiome. You can go back and study these through the recording, and once you get the slides and all that, but the microbiome is playing all of these important roles. And remember, we need aspects of the five pillars in order to fix leaky gut, right? You can't do it with any one of these pillars. Foods have to be a really important part. Diversity in your diet is critical, especially adding in things like polyphenols, fiber, the goal being 50 grams a day. We talked about this in one of the modules and above. Prebiotic foods, low to moderate fat intake, especially if your gut is leaky and you're looking at saturated fats. Reduce the amount of saturated fats. Omega-3 fatty acids actually reduce endotoxemia. Studies have shown olive oil can reduce endotoxemia. Coconut oil with its content of saturated fat dramatically increases endotoxemia.

So you have to be careful with that. You want to manage that if you're trying to heal your leaky gut. And then of course, eat real food as much as you can. Stress, big driver of endotoxemia. So meditation, mindfulness, nervous system, brain retraining. Michael's going to run a training and module on that. He's way better at that than I am, so I'll leave it at that. This is something you also have to do. It's a very important and poignant part of healing leaky gut. Lifestyle, getting outside, hiking. Just before doing this, I went on a beautiful three-mile walk through the forest preserves area here. It's gorgeous here right now, because it's high 50s, low 60s, sun shining, blue sky, leaves are falling. There's so much to engage with in nature, and it's just so beautiful to be outside. Not only is it relaxing and calming for the nervous system, you're gaining amazing exposure to microbes that diversify your microbiome.

So don't undersell or underestimate the impact of just going outside. It has to be done as part of your leaky gut protocol. Sleep and circadian rhythm, we talked about how important that is. Meal hygiene and then exercise. So strength training. After we get off

here, since I've already gone out and been active, I got three miles in, some steps with my weighted vest. I'm also going to go downstairs in my gym and do some resistance training. Why? Because when your muscles contract, especially against the weight of resistance, you release myokines. And there's some categories of myokines that your muscles release, these are a class of chemicals that your muscles release under stress and under contraction. These myokines actually go and express tight junction proteins and seal up the tight junction proteins. They can reduce inflammation in the gut, specifically, they can increase the growth of beneficial bacteria.

So just think about that. That is medicine right there. That's powerful medicine for your gut lining. So you have to add that in as well. Not any one of these should be done in isolation.

You have to add every one of these components to your daily lifestyle. And then of course, exposure, pets, dirt, all of that good stuff, minimal antibiotics, minimal sanitization around you, and just try to reduce toxin exposure, whether you have a good air filtering system, a good water filtering system, not bringing as many chemicals into your home, whatever that may look like, that's really important to you as well.

And then supplementation. There's a number of target supplementations that can help. We talked about the foundational supplements for gut health that we introduced in the end of the first module. So, **MegaSpore**, **MegaPre**, and **Tributyrin**. There's a webinar that's done that really explains **Tributyrin**. I've talked about MegaSpore and **MegaPre**, but just to give you an update here, **MegaSpore** is the only probiotic I'm aware of that has published clinical trials on dramatically reducing endotoxemia in as little as 30 days. And it does it through a number of mechanisms. So even without doing anything else within the five pillars, just taking **MegaSpore** alone, you can reduce endotoxemia by 60 to 70% in as little as 30 days. That's what we showed in published human clinical trials that are in a major gastroenterology journal.

MegaPre, Tributyrin, you've got information on this and maintains low oxygen environment, feeds the goblet cells, strengthens the tight junctions, promotes microbiome diversity, does a lot of underlying beneficial things to the gut, and increases endogenous butyrate production, which is really important. And MegaMucosa, sorry, feeds the beneficial bacteria. And through the use of polyphenols, the polyphenols feed acromansia, acromansia upregulates goblet cells, and turnover of the mucin layer. It also has these three amino acids that are the mucin building blocks, because you want to continuously build your mucus layer, but you need these three amino acids, L-proline, serine, and cysteine in order to rebuild the mucosa. And then, it also neutralizes toxins, because of the presence of IgG in MegaMucosa. So MegaMucosa is designed specifically to help that mucosal structure in your gut. If you have leaky gut, you suspect you have leaky gut. MegaMucosa should be really important part of pillar number five, the supplementation pillar, right?

And if you need to add additional IgG, I would highly recommend to my MegaIgG2000. This product has been studied in cases of HIV enteropathy. Remember, I mentioned HIV being a very severe form of leaky gut, where the microvilli shrink over time. It's a very aggressive inflammatory damaging leaky gut. There's been studies on this being able to support and help even HIV enteropathy and even Crohn's like inflammatory damage in leaky gut. So all on its own, it has a profound effect. When you combine it with things like Tributyrin, the amino acids, the polyphenols, and the MegaSpore, it becomes a very, very powerful combination for leakiness in the gut. Other supplements to consider. Polyphenols, if you're getting it as fruits and vegetables, fantastic. Try to eat about a pound, I said of berries, a variety of berries, blue, blackberries, cherries, and so on.

You'll get a good amount of the polyphenols, you'll get about how much you need. But if you want to supplement, using phenolic compounds from things like pomegranate extract has been shown clinically to reduce endotoxemia. You need about 650

milligrams per day of a phenolic extract from something like pomegranate, right? So you could look that up. Zinc carnosine can be very helpful as well. You need 75 milligrams two times a day to meet the clinical dosing to get zinc carnosine to support and help. This can help the repairing of the gut lining and reduce GI inflammation. Zinc, of course, works with the immune system. L glutamine can be useful as well. It is a fuel for the enterocytes, the lining cells of your gut, but you need about five grams a day. Now, some people can be sensitive to this, so try it once or twice. If you get a lot of flushing and a lot of discomfort, you may not be utilizing L glutamine properly, so it may not be a good fit for you.

But if it does work for you, then you need about five grams a day. Much less than that, it's not really going to do anything. So make sure you get at least five grams a day. Some clinicians I know do five grams twice a day of L-glutamine. Remember, immunological responses get completely corrupted in a leaky gut in somebody with dysbiosis. So quercetin can play a really important role here. You can reduce gut inflammation, stabilize immune responses, and thereby strengthen the tight junctions. But you'll need about 500 to a thousand milligrams of quercetin per day to that effect, right? And N-Acetyl Glucosamine NAG can also be really beneficial here by boosting mucin production that can protect and repair the lining in the gut. But you need about 500 to a thousand milligrams of that as well. You can find different products online that have these ingredients. Some of them will be standalone.

Marshmallow root has some studies on it, but I know clinically a lot of friends of mine who are practitioners use it quite a bit. A couple of the studies do support that it is beneficial, especially to soothe some of the inflammation and irritation on the lining of the gut and promote healing. But I like the liquid form of marshmallow root, but two to five milliliters per day tends to be enough of a high concentration extract of marshmallow root, and then DGL. DGL can be really useful. It's soothing to the lining of gut, reduces inflammation and can protect the mucosal layer. You need about 350 milligrams of DGL taken before a meal, three times per day. So this one is taken with

meals, but before the meal. 15 to 20, 30 minutes before the meal, if you can swing it. And that brings us to the very end of this.

I hope this made sense. What I really, really want you to get out of this, if you go back and watch this again, is really start to understand some of the physiological elements of the barrier system of the gut, what role the microbiome plays in maintaining those barrier systems, and then how endotoxemia, which is a result of leaky gut, how that drives the pathology of various diseases in the system. Even things you wouldn't necessarily connect of gut related dysfunction to Alzheimer's, Parkinson's, neurological inflammation, so type two diabetes and so on. But now you've got a lot of tools, so understand permeability. I would guess that the vast majority of people watching this who have gut issues or who have health issues probably have intestinal permeability. And there's no harm in pretending like you do, or at least assuming you do, and then doing some of the things we talked about to try to improve that permeability.

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[End Module 3]