Dr. Justin Sonnenburg: How to Build, Maintain & Repair Gut Health | Huberman Lab Podcast #62

My guest this episode is Dr. Justin Sonnenburg, Professor of Microbiology & Immunology at Stanford University. Dr. Sonnenburg's research focuses on how microbes in our gut impact our mental and physical health and how diet and your environment shape your gut microbiome. We discuss the architecture of the gut microbiome and microbiota variability in different regions of the gastrointestinal (GI) tract and how these can change in response to diet, environment or genetics. We explore the early establishment of your microbiome and how your mode of delivery into the world (C-section or not) shapes your gut. We also discuss lifestyle factors that can alter your microbiome and the integral role the gut microbiome plays in communicating to other organs, including your brain. Dr. Sonnenburg details his recent clinical study, which found that diets rich in fermented foods (but not fiber) increase microbiota diversity and reduce signals of inflammation. Additionally, we examine how foods typical in Western Diets (e.g., high fat, low fiber, processed foods) can negatively impact the gut microbiome. Throughout the episode, we discuss actionable tools from peer-reviewed clinical findings that anyone can implement, regardless of budget, in order to optimize their gut microbiome and health.

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- Welcome to The Huberman Lab Podcast, where we discuss science and science-based tools for everyday life. I'm Andrew Huberman, and I'm a professor of neurobiology and ophthalmology at Stanford School of Medicine. Today my guest is Dr. Justin Sonnenburg. Dr. Sonnenburg is a professor of microbiology and immunology at Stanford School of Medicine, and one of the world's leading experts on the gut microbiome. The gut microbiome is the existence of trillions of little microorganisms throughout your gut, and by your gut, I don't just mean your stomach. I mean your entire digestive tract. Turns out we also have a microbiome that exists in our nose, in any other location in which our body interfaces with the outside world. In fact, there's a microbiome on your skin. And while it might seem kind of intrusive, or kind of disgusting to have all these little microorganisms, they can be immensely beneficial for our health, meaning our hormonal health, our brain health and our immune system function. Dr. Sonnenburg teaches us about the gut microbiome, how it's organized spatially, meaning which microbiota live where. He teaches us about these incredible things called crypts and niches, which are little caves within our digestive tract that certain microbiota take residence. And at that premier real estate, they're able to do incredible things to support our health. He also talks about the things that we can all do to support our microbiome in order for our microbiome to support our brain and body health. Dr. Sonnenburg co-runs his laboratory with his spouse, Dr. Erica Sonnenburg, and together they've also written a terrific and highly informative book called, "The Good Gut: Taking Control of your Weight, your Mood, and your Long Term Health." Even though that book was written a few years back, the information still holds up very nicely. And today he also builds on that information, informing us about recent studies, that for instance, point to the important role of fermented foods, and the role of fiber in supporting a healthy gut microbiome. So if you heard about the gut microbiome, or even if you haven't, today you're going to hear about it from one of the world's leading experts. He makes it immensely clear as to what it is, how it functions, and how to support it for your brain and body health. During today's discussion, we don't just talk about nutrition. We also talk about the impact of behaviors and the microbiome. Behaviors such as who you touch, who you kiss, who you hug, whether or not you interact with, or avoid animals, whether or not those animals belong to you, or whether or not they belong to somebody else. If all that sounds a little bit bizarre, you'll soon understand that your microbiome is constantly being modified by the behavioral interactions, the nutritional interactions, and indeed your mood and internal reactions to the outside world. This is an incredible

system. Everyone has one. Everyone should know how it works, and everyone should know how to optimize it.

00:02:55 The Brain Body Contract

And today you're going to learn all of that from Dr. Sonnenburg. I'm pleased to announce that I'm hosting two live events in May, 2022. The first live event will take place in Seattle, Washington on May 17th. The second event will take place in Portland, Oregon on May 18th. Both are part of a series called "The Brain-Body Contract." For this series, I will discuss science, so I will discuss the mechanistic science around things like sleep and focus and motivation, physical performance, mental health, physical health, a large number of topics that I believe many people are interested in, and that certainly are important for our health and wellbeing, and performance. In addition, I will of course describe tools and actionable items, most of which I have not discussed on The Huberman Lab Podcast, or anywhere else. Pre-sale tickets for these two events go live Tuesday, Match 8th at 10:00 a.m. Pacific Time. We've made these tickets exclusively available to the listeners of The Huberman Lab Podcast. So they are password protected. To find them, you can go to hubermanlab.com/tour and use the code Huberman. Before we begin, I'd like to emphasize that this podcast is separate from my teaching and research roles at Stanford. It is however, part of my desire effort to bring zero cost to consumer information about science and science-related tools to the general public. In keeping with that theme, I'd like to thank the sponsors of today's podcast.

00:04:16 AG1 (Athletic Greens), ROKA, Helix Sleep

Our first sponsor is Athletic Greens, now called AG1. I've been taking AG1 since 2012, so I'm delighted that they're sponsoring the podcast. The reason I started taking AG1, and the reason still take AG1 once or twice a day is that it meets all my basic, foundational supplementation needs. What I mean by that is it covers any vitamin and nutritional deficiencies that I might have, 'cause I'm trying to be good about my nutrition and diet, but I don't always manage to get everything that I need, and I'm sure that there are a lot of gaps in there. So it covers those gaps. It also has probiotics, and as you'll learn in today's episode, and I've talked about it on previous episodes, the probiotics are

essential for a healthy gut microbiome. We need probiotics in order for our microbiome to thrive, and our microbiome supports things like gut-brain health, indeed things like metabolism, mood, hunger. It also that supports the immune system. As you'll learn today, your gut microbiome actually manufactures neurotransmitters, the very chemicals that impact mood and brain function. Athletic Greens primes your system for a healthy gut microbiome, something that can be achieved with food and lifestyle factors, but is often hard to achieve with just food and lifestyle factors. If you'd like to try out Athletic Greens, you can go to athleticgreens.com/huberman to claim a special offer. They give you five free travel packs that make it very easy to mix up Athletic Greens while you're on the road. And a year's supply of vitamin D3 K2. vitamin D3 has many important biological functions that support your media and long term health, and K2 as well is very important for things like cardiovascular health, calcium regulation and so on. Again, if you go to athleticgreens.com/huberman, you can claim the special offer of the five free travel packs and the vitamin D3 K2. Today's episode is also brought to us by ROKA. ROKA makes eyeglasses and sunglasses that I believe are of the very highest quality. I've spent my lifetime working on the biology of the visual system, and I can tell you that the biology of the visual system has a lot of mechanisms in there. So that for instance, if you move from a bright environment to a dim environment, your visual system needs to adapt. One issue with a lot of sunglasses and eyeglasses is you move from one environment to the next, you have to take sunglasses or eyeglasses off, you get a glare or you have to adjust because of the way that the lenses are designed. With ROKA, they've taken the biology of the visual system into account, and so you never have to take them off and on in order to move from one environment to the next. They are also designed for movement and athletics, or you can wear them for just things like work, and going out to dinner and so forth. They have a terrific aesthetic, they're extremely lightweight. In fact, I often forget that they're even on my face. I wear sunglasses when it's very bright and when I'm driving into sunlight, I wear readers at night. I hardly ever remember that they're on my face. They also won't slip off your face if you use them when running or cycling. The company was developed by two all-American swimmers from Stanford. So everything about these sunglasses and eyeglasses was developed with performance in mind, in a lot of different situations and scenarios. If you'd like to try ROKA, you can go to roka.com, that's R-O-K-A .com, and enter the code huberman to save 20% off your first order. Again, that's ROKA, roka.com, and enter the code huberman at checkout. Today's episode is also brought to us by Helix Sleep. Helix

makes mattresses and pillows that are designed for your particular sleep needs. What I mean by that is you can go to the Helix site, you can take a very brief two or three minute quiz, ask questions like do you sleep on your side, your back, your stomach, do you tend to run hot or cold through the night? Maybe you don't know the answers to those questions. And then they match you to a mattress that's designed for your particular sleep needs. I matched to the Dusk, D-U-S-K, mattress. I like a mattress that's not too firm, not too soft. I tend to sleep on my side, or sort of in the crawling soldier position. Seems to be the the most common position I sleep in. And that really works terrifically well for me. But you need to take the quiz to see which mattress works best for you. So if you're interested in upgrading your mattress, go to helixsleep.com/huberman, take the two quiz and they'll match you to a customized mattress. You can figure out how to get your optimal sleep, which was talked about on this podcast so many times before. Sleep is the foundation of all mental and physical health, and performance in any aspect of life. Sleep is key, and the mattress you sleep on is key to the sleep you get. After matching you do a customized mattress, you can get up to $200 off any mattress order and two free pillows. Again, if you're interested, you can go to heli sleep.com/huberman to get up to $200 off

00:08:30 What is the Gut Microbiome?

and two free pillows. And now for my discussion with Dr. Justin Sonnenburg. Justin, thanks so much for being here. - Great to be here. - Yeah. I am a true novice when it comes to the microbiome, so I'd like to start off with a really basic question, which is, what is the microbiome? I imagine lots of little bugs running around in my gut and I don't quite like the image of that, but I'm aware that our microbiome can be good for us, but we can also have an unhealthy microbiome. So if I were to look at the microbiome at the scale that I could see the meaningful things, what would it look like, and what's going on in there? - Yeah, I mean essentially you're correct. I mean, we have all of these little microorganisms running around in our gut. I think, just to start off with clarifying terminology, microbiome and microbiota quite often are referred to, or used to refer to our microbial community interchangeably, and I'll probably switch between those two terms today. The other important thing to realize is that these microbes are not just in our gut, but they're all over our body. They're in our nose, they're in our mouths, they're on our skin. And so basically anywhere that the environment can get to in our body,

which includes inside our digestive tract, of course, is colonized with microbes. And the vast majority of these are in our distal gut and in our colon, and so this is the gut microbiota or gut microbiome. And the density of this community is astounding. I mean, it really is. If you get down to the scale of being able to see individual microbes, you start off with a zoomed out view and you see something that looks like fecal material that digest inside the gut, and you zoom in, and you start to get to the microscopic level and see the microbes. They are just packed side to side, end to end. It's a super dense bacterial community, almost like a biofilm, something that's just made up of microbes, to the point where it's thought that around 30% of fecal matter is microbes, 30 to 50%. So it's an incredibly dense microbial community, we're talking of trillions of microbial cells. And all those microbial cells, if you start to get to know them, and see who they are, break out in the gut probably to hundreds, to 1,000 species, depending upon how you define microbial species. And then most of these are bacteria, but there are a lot of other life forms there. There are archaea, which are little microbes that are bacterial-like, but they're different. There are eukaryotes. So we commonly think of eukaryotes in the gut as something like a parasite. But there are eukaryotes, there are fungi, there are also little viruses. There are these bacteriophages that infect bacterial cells. And those actually outnumber the bacteria, like 10 to one. So they're just everywhere there, they kill bacteria. And so there's these really interesting predator/prey interactions. But overall, it's just this really dense, complex, dynamic ecosystem. And so, we're talking about the human as a single species, but we're also thinking of the human as this complex, integrated ecosystem of hundreds to thousands of species, interacting concert to do all the fantastic things that we know happen in the human body. - Amazing. So we've got a lot of cargo. Or maybe we're the cargo. - Yeah. - Who knows? - Yeah, I mean, there have been people that have likened humans to just a really elaborate culturing flask for microbes, and that we've actually been designed over the course of evolution, designed to just efficiently propagate this microbial culture from person to person, from generation to generation.

00:12:49 Gastrointestinal (GI) Tract & Microbiota Variability

So it's a different way of thinking of the human body. - Interesting. I believe that our pH or the pH of our digestive system varies as you descend, as you go from mouth to throat and stomach. And you said that most of the microbiota are in the distal colon. Are there

distinct forms of microbiota all along the length of the digestive tract, and within these other interfaces with the outside world? - Totally. Yeah. So it starts with our teeth and in our mouth, and saliva, there's a oral microbiota. These microbial species are very different than the ones that you find in the digestive tract. They're usually built to deal with oxygen very well. They're in an area that is exposed to a lot of oxygen, they of course see different nutrients than, for instance, the colonic bacteria would see. And they grow quite often in mats that live on teeth. So they're very structured in terms of... And not moving around a lot. So they're very, fairly stationary. As you move down the digestive tract, there are microbes in esophagus in our stomach, but those communities are not very dense, and actually not very well studied. We know of a very... There's a very famous stomach bacteria known as Helicobacter pylori, which can cause stomach ulcers and cause gastric cancer in some less frequent situations. But this is a very different set of microbes, they have to be adapted to a different environment, in the stomach especially, incredibly acidic environment. But also very different in terms of their ability to interact with other microbes, just because the communities are less dense, they're less dynamic, there's less nutrients that stay there and passage through the community. So a lot of times those communities are reliant upon nutrients derived from the host, as opposed to nutrients derived from our diet. As you move down out of the stomach, into the small intestine, you start to see these communities, which are the ones that are becoming more well-studied. Small intestine is still a bit of a black box, just because it's hard to access. And so there's some really cool technologies out there for using, for instance, capsules to do sampling as the capsule passes through the digestive tract, so that we have a better idea of what's going on in the small intestine. And then you get to the colon, and this is the community that's just so incredibly densely packed, doing a ton of... There's a ton of metabolic activity happening there, and a bunch of interaction with the host. And that's the community that's really the best studied. Part of the reason for that is because stool is so easy to obtain compared to, for instance, something in the stomach or small intestine. And that stool is fairly representative, we know, from studies that have been done using colonoscopies and so forth. Stool is fairly representative of what's happening in the colon. So dense, super exciting community, but also the best studied, just because it's the easiest to access

00:16:00 Breast Feeding, C-Sections & Pets

in the lower digestive tract. - Very interesting. I imagine these microbiota have to get in there at some point, are microbiota seen in newborns? In other words, where do they come from? And dare I ask, what direction do they enter the body? Or is it from multiple directions? - Yeah, yeah. Great question. So one of the burning questions that we can come back to at the end of this, is where does our microbiota come from? Because it is this kind of existential question in the field, like where is this community assembling from? And the reason that it's such an interesting question is that, a fetus, when it's in the womb, that's actually a sterile environment. There have been some studies that have looked at whether there are microbes in the womb, and microbes colonizing the fetus at that point. There's some debate about this, but overall it looks like that's not a big part of the equation of microbial colonization. And so each time I'm an infant is born, it's this new ecosystem. It's like an island rising up out of the ocean that has no species on it, and suddenly there's this land rush for this open territory. And so we know that infants go through this really complex process of microbiota assembly over the first days, weeks, months, years of life. And then you get into switching to solid food, two to three years of age. There are some changes in childhood, adolescence, working into adulthood. But that first zero to one year is a super dynamic time with really kind of stereotypical developmental changes in the gut microbiota, that appear to have the possibility of going wrong and causing problems for infants in some instances. But if you step away from that extreme side of things going wrong, there also were a lot of different trajectories that developmental process can take, because our microbiota is so malleable and so plastic, and those trajectories can be affected by all sorts of factors in early life. So an example is whether an infant is born by C-section or born vaginally. We know from beautiful work that's been done in the field that infants that are born by C-section actually have a gut microbiota that looks more like human skin than it does like either the birth canal, the vagina microbiota, or the mother's stool microbiota. Babies that are born through the birth canal have initial colonization of vaginal microbes and of stool microbes from their mother. And so just these first days, whether you're born by C-section or through natural childbirth, your gut microbiota looks very different. And then compound on top of that, whether you're breast fed or formula fed, whether your family has a pet or doesn't have a pet, whether you're exposed to antibiotics, there are all these factors that really can change that developmental process, and really change your microbial identity, eventually in life. The reason that the field is paying really close attention to this and studying this right now is because we know from animal studies, that depending upon the microbes

that you get early in life, you can send the immune system or metabolism of an organism or other parts of their biology in totally different developmental trajectories. So what microbes you're colonized with early in life can really change your biology, and we can come back to that later, but- - Yeah, we should. - Getting back to that original question of where do your microbes come from, you'd think because you're born through your mother's birth canal, or exposed to her skin microbes, that a lot of your microbes would come from your mother, but it actually turns out that, we can certainly detect that signal, we certainly see maternal microbes in the infant, but there are a lot of microbes that are coming from other places, surfaces, other people, perhaps other caregivers, but perhaps strangers as well. So we acquire our microbes from a variety of sources. The first ones are from our mom, or from our caregivers from the hospital, but then we add to that tremendously over the first year or so of life. - Incredible, you even said pets. So if there's a dog in the home or a parakeet in the home, clearly they have a microbiome also, and potentially the child is deriving microbiota species from those pets, correct? - Exactly, yeah. And so the best studies that have been done have just looked at pets in the household as a factor, and whether that changes the group of infants that have a pet to look slightly different than the group of infants that don't have a pet. And then the question is, what is the pet doing to change those microbes? And some of it is probably actually contributing, direct members of the microbiota. Actually, I have a dog, that dog occasionally will lick my mouth without me paying attention, and that's probably introducing microbes. We also know that pets are down in the dirt, they're outside, they're being exposed to a lot of environmental microbes. And so just pets serving as a conduit for a bunch of microbes that we wouldn't otherwise come in contact with is a possibility as well. - Well, we will return to pets, and in particular your dog, an amazing dog, by the way. I met your dog just the other day, and I had to force myself, I had to pry myself away from... It's a Havanese, right? - Havanese. - [Andrew Huberman] Incredible. What is your dog's name? - Louis. Louis Pasteur. - Louis Pasteur. - Yeah, yeah.

00:21:56 The Human Microbiome Project at Stanford

- How appropriate. Amazing dog, what a personality on that dog. - Yeah. - The issue that I think a lot of people are probably wondering is, what is a healthy microbiome? What is it supporting? We hear that you need a healthy microbiome to support the immune system or metabolism, or even the gut-brain axis. How do we define a healthy, versus a

unhealthy microbiome? Some people might know the unhealthy microbiome is dysbiosis is the word that I encounter in the literature. But given that there's so many species of microbiota, and given that I think we probably each have a signature pattern of microbiota, how do we define healthy versus unhealthy microbiota? Is there a test for this? Later we'll talk about technologies for testing microbiota. There are a lot of companies now, a lot of people sending stool samples in the mail. Never look at the Postal Service the same way again, but it's out there and it's getting analyzed. So how should I think about this? I can think about things like heart rate, heart rate variability, BMI, all sorts of metrics of health. How should I think about the microbiota? How do I know if my microbiome is healthy or unhealthy? - Yeah, it's a million dollar question right now in the field, and there's a lot of different ways of thinking about that, and I can talk about some of those. But I would say that there are sessions at conferences, there are review articles being commissioned. There are all sorts of thought pieces about this right now, like what is a healthy microbiota? What are the features that define it? And I think before diving into this, the important thing to realize is, it's a complex topic. Context matters a lot. What's healthy for one person or one population may not be healthy for another person or population. And the microbiota is malleable. It's plastic, it changes our human biology, which I think is, how we think about health quite often, BMI and longevity, reproductive success, however you want to define it. It certainly can accommodate a variety of configurations of gut microbiota, and we don't have... It's really hard to untangle all of the different factors of what could be very healthy, versus a little bit less healthy. So I will say that there's no single answer to this, but there's some really important considerations. And perhaps the best way to start talking about this is to go back to the inception of the Human Microbiome Project, which was this program that NIH started. They invested a lot of money in 2008, 2009 for really propelling the field of gut microbiome research. It was becoming evident at that point that this was not just a curiosity of human biology, that it was probably really important for our health. And they had all this wonderful sequencing technology from the Human Genome Sequencing Project, and with the human genome completed that point, they started turning that technology to sequencing our gut microbes. And it's important to contextualize the amount of information that they're trying to document, the collective genome of our gut microbes is on the order of 100 to 500 times larger than our human genome. So it's just in terms of the number of genes. So it's just this vast number of genes, and then if you start getting into some of the fine variation, it's scales by 10 to a 100 fold. So really a

huge amount information they're trying to document. And so it was a wonderful investment, and it continues to pay dividends to this day. But one of their goals of that project was to try to define what a healthy microbiome is, versus a diseased microbiome in different contexts. And so they started enrolling a bunch of healthy people and a bunch of people with, for instance, inflammatory bowel disease and other diseases. And the idea was, let's document those microbiomes. What microbes are there, what genes are there? And then we can start to get a sense of, what are the commonalities of the healthy people, and how can that go wrong in these different disease states? There were some answers from that, but through those studies, we really started to get the image that there is this tremendous individuality in the gut microbiome. And so it's really hard to start drawing conclusions

00:26:30 Traditional vs. Industrialized Populations

after initial pass of that project, of what is a healthy microbiome? But the other thing that we started to realize at the same time, there were studies going on documenting the gut microbiome of traditional populations of humans, hunter-gatherers, rural agricultural populations. And those studies were really mind-blowing from the perspective of all these people are healthy, they're living very different lifestyles, and their microbiome doesn't look anything like a healthy American microbiome. - So does that mean that the healthy American microbiome is healthy, but only in the context of living in the United States and consuming what's consumed here? Or is it that there is a superior microbiome signature, somewhere in our history or currently in the world? - Yeah, I think that's kind of a big question right now. I think there's a great quote from Dobzhansky that says, "Nothing in biology makes sense, except in the light of evolution." And these traditional populations are all modern people living on the planet now, but their lifestyle does represent the closest approximation to how our ancestors, early humans lived. And so those microbiomes, and now we know from sequencing of paleofeces, the microbiome of these traditional populations is more representative of the microbiome that we evolved with, that potentially shaped our human genome. And so one possibility is that in industrialized world, we have a different microbiome from traditional populations, and that microbiome is well-adapted to our current lifestyle, and therefore healthy in the context of an industrialized society. And there probably are elements of that that are true. But another possibility is that this is a microbiome that's gone off the

rails, that it is deteriorating in the face of antibiotic use, and all the problems associated with an industrialized diet, Western diet. And that even though the Human Microbiome Project documented the microbiome of healthy people, healthy Americans, that what they really may have been documenting there is a perturbed microbiota that's really predisposing people to a variety

00:28:58 Resilience of the Microbiome

of inflammatory and metabolic diseases. - It reminds me, as a neurobiologist, was weaned in the landscape of so-called critical periods, where early life environment very strongly shapes the brain. And so many studies were done on animals raised in traditional cages with a water bottle and some food, maybe a few other animals of the same species. And then people came along and said, wait, normally these species in the wild would have things like things to climb over and things to go through, and you provide those very basic elements, and all of a sudden the architecture of neural circuits looks very different, and you realize that were studying a deprived condition. And earlier you actually referred to, if I understood correctly, to critical periods for gut microbiome development. Is it fair to say that there are critical periods? Meaning, if let's say my... Let's aim it at me. If my gut microbiome was dysbiotic, it was off early in life, can I rescue that through proper conditions and exercise? Or is there some sort of fixed pattern that's going to be hard for me to escape from? - Yeah, there's a big field that's emerging now that we refer to as kind of reprogramming the gut microbiome. And I think if we want to conceptualize humans as this aggregate human microbial biology, most people have heard of CRISPR, and the ability to potentially change our human genome in ways that correct genetic problems. That's a wonderful technology, and has kind of put on the table genetic engineering for cur disease, but it's much easier to change gut microbes for a problem, just because that community is malleable. The issue that I think we're seeing in the field is that microbiomes quite often, whether they're diseased or healthy, exist in stable states. They kind of tend towards this well that has gravity to it in a way, biological gravity, where it's really hard to dislodge that community from that state. So even individuals, for instance, that get antibiotics. You take oral antibiotics, the community takes this huge hit. We know that a bunch of microbes die, the composition changes. And that represents a period of vulnerability where pathogens can come in and take over and cause disease. But if that doesn't happen, the microbiota kind of works its way back

to something that is not exactly like, but similar to the pre-antibiotic treatment. We know with dietary perturbations, quite often you'll see a really rapid change to the gut microbiome. And then it's almost like a memory where it snaps back to something that's very similar to the original state, even though the diet remains different. And so there's this incredible, what we refer to as resilience of the gut microbiome, and resistance to change, or at least resistance to establishing a new stable state. So that doesn't mean it's hopeless to change an unhealthy microbiome to a healthy microbiome, but it does mean that we need to think carefully about restructuring these communities in ways where we can achieve a new stable state that will resist the microbial community getting pulled back to that original state. And one of the really simplest and nicest examples of this an experiment that we performed with mice, where we were feeding mice a normal mouse diet, a lot of nutrients there for the gut microbiota, things like dietary fiber. And we switched those mice, half the mice, to a low fiber diet. And we were basically asking the question that if you switch to kind of a Western-like diet, a low fiber, higher fat diet, what happens to the gut microbiota? And we saw the microbiota change, it lost diversity. It was very similar to what we see in the difference between industrialized and traditional populations. But when we brought back a healthy diet, a lot of the microbes returned, it was fairly... There was this kind of memory where it went back to very similar to its original state. The difference is that when we put the mice on the low fiber, high fat diet, and then kept them on that for multiple generations, we saw this progressive deterioration over the course of generations whereby the fourth generation, the gut microbiome was a fraction of what it originally was. Let's say 30% of the species only remained something like 70% of the species had gone extinct, or appeared to have gone extinct. We then put those mice back onto a high fiber diet, and we didn't see recovery. So in that case, it's a situation where a new stable state has been achieved. In that case, it's probably because those mice don't actually have access to the microbes that they've lost. And we actually know that we did the control experiment of mice on a high fiber diet for four generations. They maintain all their microbes. If we take those fourth generation mice with all the diversity and do a fecal transplant into the mice that had lost their microbes, but had been returned to a high fiber diet, all of the diversity was reconstituted. So your question of like, how do we establish new stable states? How do we get back to a healthy microbiota if we have taken a lot of antibiotics, or have a deteriorated microbiota, it's probably a combination of having access to the right microbes. And we can talk about what that access looks like. It may look like

therapeutics in the future. There are a lot of companies working on creating cocktails of healthy microbes. But it'll be a combination of access to the right microbes and nourishing those microbes with the proper diet. - Very interesting. This multi-generational study reminds me of something that I was told early in my training, which was that it takes a long time for a trait to evolve, but not a long time for traits to devolve. - Yeah, exactly. - Which generally is true of human behavior too, although it depends.

00:35:10 Regional Differences Along Your GI Tract

We can all do better, nonetheless. - [Justin Sonnenburg] Very interesting. - So I have a puzzle or a bit of a conundrum around this notion of species of microbiota. So if the pH, if the acidity differs along the digestive tract, but is more or less fixed for a given location, right? I mean, unless something's really off, the pH of the stomach is within a particular range, and the intestines and so forth. And certain microbiota thrive at a given station, a given location along the digestive tract, and the pH is sort of fixed more or less. I'm trying to figure out, what is allowing certain microbiota to stay in a given location? Why don't they migrate up or down? So are they pH sensitive, and that's what they're selecting for along the tract? And I'm also trying to figure out how these changes in food so robustly change the microbiome. The way you describe it almost makes it sound like food is the variable that's going to dictate the quality of the microbiome, although I'm sure there are other factors as well. And then in the back of my mind, I don't know that I want to ask this question, but I really want to ask this question, which is, where are they in there exactly, and why don't they all get flushed out? Right? - Right. - If 30% of fecal matter is microbiota, then where are they living? Are they along the lining, and the little microvilli of the intestine, and what are they attaching to and interacting with? we know there are neurons in there, especially within the stomach, there's a lot of work now being done on the gut neurons and how they signal to the brain and so forth. But who are they talking to in terms of the host cells? - Yeah. - Because if it's just from food, I imagine that they're in there having their good time, or not, and then some are getting flushed out or not, but how do they actually stay in there? - Yeah. - Who are they attaching to? What are they talking about? What are they doing for fun? - Yeah. - And so forth. - Yeah, yeah. Super interesting. So I'll come back to the attachment question, and kind of why they don't get washed out, 'cause this is a super fascinating question. And I think your initial point of like, the kind of regional differences in what's happening in terms of physiology,

biochemistry along the length of the gut is really interesting. There certainly is a pH gradient along the length of the gut. There is actually bicarbonate that's secreted into the small intestine to try to neutralize stomach acid. There also is bile that's secreted. That creates a different chemical environment in there, bio-loving bacteria that kind of live in that region of the gut. And then there is a nutrient gradient, just because as food leaves the stomach, a lot of the simple nutrients are absorbed. And so you might see microbes in the small intestine, for instance, that are better at consuming simple sugars, but you won't find many microbes in the colon like that, because all the simple sugars have been depleted at that point. And then the immune system is a big factor as well. And the immune system is incredibly active in the small intestine. The small intestine is this really interesting challenge for the host, because it's a tissue that's been... Its purpose is mainly absorptive. And so there has to be flow of a lot of things, a lot of nutrients from the luminal contents into host cells. And so that means the barrier can't be as fortified. And so the immune system is incredibly active in the small intestine to make sure that microbes aren't getting so close, and if they are getting close, there's a response to them to put them back in their right location. And then along this whole kind of architecture of the gut, there's the longitudinal gradients, things like pH and so forth. And I should say that pH starts to drop again in the colon, because a lot of those microbes are fermenting things and producing acids. And so you actually end up with the pH starting to drop, not as low as the stomach, but starting to drop again if there's a lot of fermentation happening in the colon. In addition, you also have a gradient from the host surface epithelium out to the middle of the gut. And that is likely the key for what is retained in the gut and how the community isn't washed out. So lining the gut, we have epithelial cells. In the small intestine, they're largely absorbative. In the colon, there's a lot of mucus production. And we also see this in the small intestine, and this mucus lining is this substance that we secrete, largely made of carbohydrate actually. And the purpose of that is to keep microbes in the right spot and to allow nutrients and water to be absorbed in the small intestine and large intestine. And so it's this mesh work that is supposed to keep out large things like back to and lead, and small things like nutrients. That mucus layer is, it turns over more slowly than the luminal contents passing by. And so if a microbe learns to hold onto that mucus layer, it can actually resist the flow of the contents of the gut. And so there there's many microbes in the gut that are not just good at attaching to mucus, but also good at nibbling on it, at eating it. And there are these bacteria, like Akkermansia muciniphila, mucus-loving. One of its main things it does is

actually eat mucus in the gut, that's its lifestyle. And so there's an incredible gradient of activity from the host tissue, working your way out to the middle of the gut. What's amazing is some microbes actually do penetrate past the mucus, and there are these invaginations in the intestine known as crypts, actually where the stem cells live that produce the epithelium, and there are microbial communities that can form in those crypts. And we don't know completely what their function is, but we've done some studies that appear to indicate that if you can localize to a crypt, you've hit the jackpot as a microbe for being able to maintain dominance in the gut. So if you sit in the crypt and something similar to you, another microbe that's similar to you, comes into the gut, you can actually exclude that microbe. And the thinking is that it can't find a spot to resist being washed out of the gut. So there probably are these little niches close to host tissue in the mucus that are absolutely essential for resisting getting washed out

00:42:04 Fasting, Cleanses & Gut Health

with the flow of all the contents. - Incredible. That raises a question about two things that are reasonably popular. One is this notion of cleanses, from either direction. People will consume things by mouth to try and cleanse their digestive tract. This there's a long history of this. I'm not recommending this. There's differing opinions on whether or not this is good or bad. And the other is fasting or time-restricted feeding. The reason I ask about time-restricted feeding, is my understanding is that after a prolonged period of fasting, there's some auto-absorption or digestion of one's own digestive tract, that then gets renewed. In other words, you're testing and stomach start eating its own lining to some extent in the absence of food. So what do we know about cleanses? Oh, and then I suppose there's cleanses from the other direction too, right? Which, less popular, but I've never run the statistics, but certainly exist out there. What's the idea about cleanses and fasting as it relates to the health or the dysbiosis of the microbiota? - Yeah, there hasn't been a lot of high quality science in this area, and so it's really hard to conclude whether these are good for health or bad for health. I think the fasting... We're in a really interesting situation in the industrialized world, because we have so many problems associated with our digestive tract, and that probably has to do with our highly processed diet and perhaps having a microbiota that's fairly perturbed as well. And so, whether doing things like this are good or bad, it's really hard to define, because we may be starting off in a fairly bad state anyway. There's so many diseases that we're dealing

with, metabolic syndrome, inflammatory bowel disease, that just put a massive portion of the population in a very different category than people that are thinking about how do I maintain health, how do I live a long life, from starting off in what we consider a fairly healthy state. And so things like fasting and a lot of other therapies that have been developed in the field, I think ketogenic diet may be in this category as well. There can be tremendous benefits in terms of their impact in the context of metabolic syndrome, and for people that are battling eating a continual bad diet or something like that. - And adherence. I think one of the one of the reasons for the popularity of intermittent fasting, time-restricted feeding, and what do they call them now? Exclusion diets, where you entire entirely exclude meat, or you entirely exclude plants or whatever it is, is that adherence is sometimes easier in the all or none. As neurobiologists, we think of it as a go, no-go circuitry. It's harder to make decisions, nuanced decisions often, about food than it is to just eliminate entire categories of food. Not eating, for many people- - Yeah. - Is easier than eating smaller portions. - Yeah, yeah. Yeah, and- - Yeah. So some of it, I think, is neurobiological and psychological. - Absolutely. And we've had gastroenterology fellows in our lab that come in and we kind of... I think that to kind of slice through the nuance of all this, there's a very simple recipe and a really well accepted, broad definition of what a healthy diet is. kind of the Mediterranean diet, plant-based diet is... There's just a ton of data that particularly people of European ancestry, but there's a pretty broad acceptance that if you eat mostly plants, for most people, that's going to be very healthy, to the point where... A wonderful colleague of ours, Christopher Gardner, who's studied diet his whole life, trying to establish what a healthy diet is. And people was giving advice, I saw him giving advice to a dietician who is trying to get all the rules of what she should be recommending to people that she deals with that are interested in a healthy diet. And she said, so the number one, I'm going to say, plant-based fiber is probably super important, and that should be very high on the list. And she goes on to number two and he said, stop. He said, if people do number one well, you don't need to know any other rules. I mean, it's basically like if you can have a high fiber, plant-based diet, for most people, at least, talking about the bucket of people that are already in a healthy state, you don't really need to think about other things, because you can't eat too much meat, you can't eat too many sweets. You've already eaten a huge amount of plant-based fiber. Your gut is full, you're not going to be hungry. And it kind of takes care of worrying about what should I eat or what, what shouldn't I eat. Just eat a ton of whole grains, legumes, vegetables, fruit that's high fiber based, not high sugar. - Does it

completely exclude meat, and fish and dairy? - And he was saying people can add their own spins on this. But I think that the main rule is just start off with... And it kind of gets back to, to Michael Pollan's mantra, eat food, not too much, mostly plants. I think if you stick with these simple rules, and don't overthink, like, should I have this? Can I eat eggs? Can I eat... Just kind of stick to these simple rules, it makes it very approachable. But I agree, so these gastroenterology fellows that we've had in our lab say that they... It's really hard. We kind of say to them, why won't you give this dietary advice that's really well-known. And they just said, well, it's, it's really hard to get people to change their diet, unless you're doing either a go, no-go sort of thing, or eliminating something. So if carrots are giving you problems, don't eat carrots. And that's a very simple, easy instruction to follow, but doesn't really deal with the root problem of why can't you eat carrots, because you should be able to eat carrots. Most people can eat carrots. And so I think that we... Yeah, when we're thinking about things like fasting, and all these different dietary regimes and cleanses that people do, we have to step back for a moment and say, okay, well, what are really the big, high level rules that we should take home? And then if you are experiencing problems, and you want to think about how to deal with them, it's good to go to an evidence-based method where there's actually data to back it up. The data in the field really shows that with like fasting, particularly if you go to animals that hibernate, or things like that, where there's really extended fasts, you actually have a microbiota come up that blooms in the absence of food coming in through diet that's really good at eating mucus. So you have bacteria that's that specialize in eating nutrients derived from the host, because there's no other nutrients to live on. Now, whether this is good or bad, we don't know. But it seems like the consumption of mucus in excess is a problem from the standpoint of microbes getting too close to host tissue and inciting inflammation, which is what we see in animal models when we deprive of dietary fiber. We see these mucus utilizers become abundant, and inflammatory markers start to come on. So fasting short term might be fine, probably. There's definitely benefits that are seen metabolically. In terms of what it means for long term health from the standpoint of the gut microbiota, I would say we don't have the answer to that yet. In terms of the cleanses and the flushes and all this, personally, I think it's a terrible idea. I mean, we know that if... In studies that are being done now to reprogram the gut microbiota to install a completely new microbial community, the first step is to wash away the resident microbial community that's there. So if you're in the process of acquiring a really good microbiota and you know how to do that, then flushing

everything out is great. Otherwise, what is happening is you're kind of leaving rebuilding of the community to chance, like what is it? And so what microbes are going to colonize? Who's going to take up space after you do this flush or cleanse? And I think it's a little bit like playing Russian Roulette. You may end up with a good microbial community in there afterwards, you may not. You certainly want to pay close attention to what you're eating while you're doing the reconstitution of the community after you do something like that. - Yeah. Thank you for that. I know a lot of people are interested in these kinds of elimination diets. And intermittent fasting/ time-restricted feeding seems to be getting some traction, in part, because at some level we are all doing this when we sleep. Most of us aren't eating while we sleep anyway, and adjusting the numbers seems more accessible for a lot of people. We have a lot of colleagues at Stanford who I know happen to of that regimen, or a time-restricted feeding regimen,

00:51:19 Dietary Differences

but also who follow the more traditional meal spacing as well, of course. One of the things that I wonder about as we talk about primarily plant-based with some, what did you say the Pollan thing was? It was eat mostly plants and then maybe some meat, but not too much, or not too much... - Yeah, eat food, mostly plants, not too much. - Got it. - Or sorry, eat food, not too much, mostly plants. - Got it. I hear this again and again. I know there are a number of people who do seem to do well on a lower carbohydrate, and even some people who report feeling much better on a really strictly, almost meat, organ-only diet. And the only reason I raise is not... I don't participate in... I'm one of those omnivores that out there, I do eat some meat and I do eat plants as well. But the reason I raise this is that earlier you were talking about communities that may have microbiota that are healthier than ours, or at least different than ours. And there are communities in the world that subsist largely on animal products, or for which unprocessed animal products are considered the richest-nutrient foods in those communities. Protein is very scarce in... Ancestrally, protein was more scarce, so eggs and meat and things of that sort. So could there be a genetic component? In other words, if we fast forward 10 years and we actually can make sense of all this human genome stuff, are we going to find that someone who has Scandinavian roots, or somebody who has South American roots, or somebody had descended from a different tribe, will do better on one particular diet versus another, and thereby, or I should say,

and in parallel with that, that their gut microbiome will have different signatures that are... So your microbiome might thrive on plants and mine might thrive on organ meats. And as I say this, I'm not a big consumer of organ meats. I'm just laying this out for sake of example. - Yeah. Yeah, great. So, a few notes, the first one has to do with carbohydrates and restriction of carbohydrates, and some people feeling healthier when they cut carbohydrates out. My guess is... This is my theory to be tested, that people feel better cutting carbohydrates out, because the diet that we eat in the United States and in industrialized countries, the carbohydrates are largely crap. - Processed. - They're processed. - Right. - It's like starch, simple sugar. It's things that contribute to glycemic index. It's these sugars that we eat. They make it to our small intestine, they get chopped up into simple sugars, absorbed into our bloodstream, and we have a ton of glucose then coursing through our veins, which we know is bad and can lead to things like diabetes. If the carbohydrates that were in our diet were complex carbohydrates, dietary fiber, and we like to refer to the subset of dietary fiber that the microbiota can actually access as microbiota-accessible carbohydrates. And the reason that we like that term is it has the word carbohydrate in it. And it's to point out that not all carbs are bad, it's just, there are bad carbs or carbs, or carbs that are bad if you consume them in too high quantity, things like table sugar and simple starches, but there are good carbs as well. And these microbiota-accessible carbohydrates are the complex ones that we can't digest, and fuel our got microbiota, our gut microbiota can ferment them. I think we probably all would be better off with less of the carbs that we're typically served, but most of us, and probably the vast majority of us would be better off by consuming a lot more carbs that were complex, that we're microbiotic-accessible. And I'll come back to why that's important in terms of our biology. There's some mechanisms that are known as to why those complex carbohydrates are so important for our health, for most of us. I think this aspect of human genetic adaptation to diet is super interesting. And then layer on top of that got microbiota adaptation to diet, which is another layer of this that is also fascinating. It's very clear that over very short periods of time, humans can adapt to differences in their diet, lactase persistence as kind of the classic example of this. Just over the past 10,000 years, certain groups of humans have adapted to being able to consume dairy by taking this enzyme, lactase, that normally is just expressed in most of the world's population early in life to be able to metabolize lactose in breast milk. By extending the expression of that throughout life, now you can consume milk for your whole life. And so that is an example of specific populations of human genome,

genetically adapting to diet in a very short period of time. And there are other examples of this, and undoubtedly, this has happened throughout the world to various aspects of diets. So certainly it's important to remember that there will be different diets that are better for different groups, based on what genes you harbor and have in your human genome. The other aspect on top of that is that, there are good examples of the gut microbiome adapting to cultural differences in diet. And the classic example of this is the degradation of seaweed. So we know that most Americans, if you eat sushi, and there's nori there and you eat some of the seaweed, it has a dietary fiber in it known as porphyrin. That porphyrin will shoot through most of us untransformed. Inert substance. It'll do other things like retain water, and serve as kind of something like cellulose, not be fermented at a high level. If somebody from Southeast Asia that's always consumed seaweed, and is part of a culture that consumes seaweed, eats seaweed, they have a gut microbe that can now metabolize porphyrin. And so there are these very specific gene transfer events where the genes for breaking down porphyrin have been imported into the microbiome of many people in Southeast Asia to... We can think of it as helping digest porphyrin, but it's really just a microbe that's found a niche, found a way to make a living in the gut by consuming something that's common in the diet there. So there are these different layers, there are human genetic adaptations, and there are microbiome adaptations that are cultural, and based on people's geographic location. But there's no escaping the fact that for much of human evolution, the vast majority of people that are on this planet had ancestors that were hunter-gatherers, foraging, consuming huge quantities of plant material, just because that's what was there. And so one of the groups that we study, the Hadza hunter-gatherers in Africa, and I should take a moment just to say that our research, and research of many people in our field and other fields rely on study of indigenous communities. And it's really important to think of these communities, as our equals, they're modern people on the planet. They have interesting lifestyles that are informative with regard to certain aspects of human biology, but in many cases, they also are leading a vulnerable existence. And so we really take great care in our research program, and it's important for people to realize that these populations take part in our research, because they're wonderful research partners. And we need to be mindful of kind of thinking about how, yeah, both we talk about them and use our data that has been gained through their generous contribution to our research program. The Hadza hunter-gatherers, it's estimated, consume on the order 100 to 150 grams of dietary fiber per day, and that's in stark contrast to the typical American that consumes about 15

grams. So somewhere, a seven to tenfold decrease in the main nutrient that feeds are got microbiome in the American diet. The Hadza are one example. There are many different foraging populations, but the vast majority of these populations consume huge amounts of dietary fiber, because plants are the reliable, consistent source. If you, as a hunter-gatherer go on a hunt, usually that hunt is unsuccessful. I think the data that one out of 20 hunts are successful in landing actually big game for the Hadza. They have birds that they shoot and small animals, but quite often, day after day, they're relying upon berries, tubers, baobab fruit. They're relying on the plants in their environment. And actually if you go to the data and look at what their fruit food preferences are, their food preferences are actually meat and honey. So they don't eat a high fiber diet because they love fiber. They eat a high fiber diet, because that's what's available and consistent for them to survive. But our brains are wired for caloric density. And so if you took a Hadza and put them in a restaurant in the United States, they would make the same crappy decisions that we make, because we all want sugar and fat and calories. It's how our brain is wired. - And protein and fat for brain development, as far as we know, right? So it sounds like the Hadza, I hope I'm pronouncing that correctly, you said would prefer to eat meat and honey, but they happen to consume a lot of plant fiber

01:01:24 Simple vs. Complex Carbohydrates, Processed Foods

as a consequence of what's available. One of the questions I have as it relates to all of this, is it sounds to me like there is no question from the pure vegan all the way to the extreme opposite, which would be pure meat diet, that avoiding processed foods is a good idea. - Yeah. - Or heavily processed foods, in general and I mean, not that the occasional consumption is necessarily bad. But whether or not one is thinking about one macronutrient profile or another, it sounds like consuming processed foods is just bad for the microbiome. Can we say that categorically? For sure, yeah, yeah. - Okay. - Absolutely. - So you're a low carb person, you're a zero carb person, you're extreme vegan, no meat. Whether or not you're all meat, organ meat. Sounds to me as if the number one thing, maybe even, dare I say above Chris's point about plants, although I'm not going to challenge Chris Gardner on nutrition, I would be way outside the lane lines to do that. But is it to avoiding processed foods? - Yeah. - Is paramount. - Yeah, and I think that's completely compatible with what Christopher was saying. He was saying, if you prioritize getting a huge amount of whole, plant-based food with a lot of fiber first,

you're not going to have room for eating a lot of processed food. - [Andrew Huberman] Yeah, yeah. - So it's kind of the same as avoiding processed food. So I think that those are exactly the same rule, and I think that you're exactly right. And we can break down... There's a lot of data of why different components of processed food are so bad for us, and so bad for our microbiome. And I can talk about a few examples of that. But the flip side of this is this mechanism of... And again, thinking about the spectrum of a plant-based diet versus a meat-based diet. There's a lot of data to tell us that a meat or ketogenic, or high fat diet may have big benefits in terms of short term metabolic health. That's typically how people think about that diet. There's also a lot of heart disease that's linked with that as well. There's good literature for that, which is something for people to look at and be aware of. The plant-based diet, if you're eating a bunch of complex fibers that feed your gut microbiota, your gut microbiota produces these substances called short-chain fatty acids, things like butyrate. And it's known that these short-chain fatty acids play really essential components, both in terms of fueling colonocytes, enforcing the barrier, keeping inflammation low, regulating the immune system, regulating metabolism. And so a lot of people think of dietary fiber as this inert substance that passes through, makes this feel full maybe for a little bit, but we get hungry afterwards right away. If you're eating a lot of fiber that's feeding your gut microbiota, your gut microbiota is just producing this vast array of fermentation end products that then get absorbed into our bloodstream, and have all of these tremendous, cascading effects that appear to be largely beneficial on our biology. And so to think about that paradigm of simple carbs, versus complex carbs, in the case of simple carbs, you end up with high blood sugar, something that will spike your insulin, and have all kinds of weird, metabolic effects. In the case of complex carbohydrates, you'll end up with very low blood sugar, because most of those have low glycemic index and a bunch of short-chain fatty acids that are having regulatory roles. So just to round out that topic, I think there is a reason to think that, maybe not appropriate for absolutely everyone out there, but I think the vast majority of people, particularly given the statistics of what we know people eat in the United States and in industrialized countries, most people would reap tremendous health benefits from eating more whole, plant-based dietary fiber. Now, processed foods, I think, is this other dimension where you have all of these weird chemicals, artificial sweeteners, weird fats, a lot of refined, simple nutrients. The simple nutrients we've talked about, but we know that for instance, artificial sweeteners can have a massive negative impact on the gut microbiome and can lead us towards metabolic syndrome,

actually. There's been beautiful work out of the Weizmann Institute on this. And then emulsifiers, these compounds that are put in processed foods to help them maintain shelf stability so things don't separate. And so all the the moisture content is retained appropriately. Many of these are known to disrupt the mucus layer, and as soon as you start disrupting that barrier, that can lead you in the direction of inflammation and in animal models, we know that can lead towards metabolic syndrome as well. So there's components of processed food, that are, when studied in isolation known to have a direct negative impact on gut biology in the microbiota. - Yeah, the mention of artificial sweeteners interesting. I confess it's a third rail on... Talking about artificial sweeteners, there are two camps it seems, or at least two camps. One that say artificial sweeteners are not detrimental at all. Another that says they're very detrimental, mainly based on the mouse studies. And then there are people in the middle that are... I put myself in that category. I drink the occasional diet soda, I don't consume them in large volume, but I'm sort of in the middle there. And so I just throw that out there, because I know immediately people are jumping on that, but I will just mention there's some recent data out of Diego Bohorquez's lab at Duke University that the neurons that live in the gut mucose of these neuro pod cells can actually distinguish between artificial and true sweet... Sugar versus artificial sweeteners. They send different patterns of neural signals up to the brain, and the brain circuitry seems strongly impacted. So I think that as the data emerge,

01:07:03 Artificial & Plant-based Sweeteners

we're hearing more and more of these artificial sweeteners. Either are problematic or at least are signaling different events in the gut. I do want to make sure that we distinguish artificial sweeteners from non-caloric plant-based sweeteners. - Yeah. - And this is based on a mistake that I've made over and over again on the podcast where I'll just kind of lump artificial sweeten into one big category, and then I'll mention stevia. So what about plant-based sweeteners that are not artificial, they weren't manufactured in a laboratory, like saccharin or sucralose, or aspartame? Do we know anything about plant-based, non caloric sweeteners or low caloric sweeteners? - Very little. A lot of those have a lot more bang for the buck. They're incredibly sweet, so it takes a really small amount for them to trigger a huge amount of sweetness. And so it's, depending upon the mechanism of action by which these sweeteners that are not sugar are impacting our

biology. It may be that those are actually less negative or more healthy than the ones that are artificial, just because it requires less of them in the food for us to perceive that sweet taste. It may also be that because they're... I don't think that everything is that's natural is better, necessarily than things that are artificial, but it may be that because of kind of evolutionary exposure to these compounds in our diet, historically there are, I think, traditional populations that use these, for instance, to sweeten different foods, that our bodies just know how to deal with those compounds better than the ones that are synthetic. But I think the studies still need to be done. - Do you actively avoid artificial sweeteners? Sucralose, aspartame, saccharin? You personally. - Yeah. So I do, I avoid them, but I'm not... So I work closely with my wife, Erica, as you know. We were in the lab together and we wrote this book, "The Good Gut," where we kind of document our journey in changing our lifestyle, dietary habits, choices we make based on the research as we've gotten to know it in the gut microbiota over the past 15 years. And I think that one of the lessons that we've learned is that just doing things in moderation makes it a lot easier, and doing things slowly makes it a lot easier. So there are very few rules that I have that are hard and fast. I'm a pretty flexible eater. I don't believe that having a diet Coke will somehow cascade into some terrible disease or something like that. I try to avoid them, I don't really like the flavor of them. I'm super sensitive to the nuances of the flavor, even with the stevia and mogrosides from monk fruit and stuff like that. The off flavors are really hard for me to deal with. But also in this journey of changing our diet... Like when we started off in microbiome research, I was in the habit of in the afternoons having a sweet, a muffin or a cookie, or something like that. And when we started to realize that we should be eating less sweets and eating more dietary fiber, this was an incredibly difficult change for me to make. I was just wired to kind of crave this- - Classic scientist. Scientists love the pastry in the afternoon and the coffee. - Yeah, yeah. - And in the old days it used to be a cigarette too. - Right, exactly. - When I started my training, a lot of people still smoked - Yeah, right. - And it was only during my post-doctoral training that they eliminate smoking on campuses, and productivity took a trough for a while, until these people developed other tools to focus their attention. - Exactly, exactly. So there is this kind of need, and then once you have an ingrained behavior, and maybe things that are addictive, it becomes incredibly difficult to break that habit. And so I would say, gradually over the course of like, five or more years, we have migrated our diet away from sweet foods to things that are less sweet. And it's been a journey, it's been a slow process, but we've gotten to the point now where we've just retrained our pallets.

And it's amazing how this happens now, where I'll have something that is something that I would've used to have like daily. And it's unpalatable. I just can't deal with the sweetness of it. And I certainly avoid artificial sweeteners, but I also avoid just sweet things in general that have sugar in them, just because they now, was originally, I was trying to be disciplined and trying to change my diet, but now they just don't taste good to me. - Yeah, likewise, I completely lost my appetite for sugar at the turn of the last year, and I don't know how to explain it, but the way I... Even though I don't have a mechanistic explanation, I say I like sweet people, I don't like sweet food anymore. I just don't. I have not lost my appetite for fatty foods. I love cheese and certain meats for me, I blame my Argentine lineage is, is I gravitate towards them. But in any case, avoiding processed foods, probably avoiding sugars, emulsifiers, these kinds of things. And for people listening or watching, we're not setting up strict guidelines. We're just bouncing around the carnival that is the microbiome and nutrition, because I think that we hear this everywhere, eat this, don't eat that, or this is best for microbiome, or worse for microbiome. But I'm hearing fiber again and again, so we're going to come back to fiber, but I want to make sure that we close the hatch on this issue of fasting and cleansing.

01:12:44 Cleanses: Useful? Harmful?

Based on your answer earlier, it sounds to me like it is not necessary to do a cleanse or fast prior to an attempt to repopulate the microbiome. In other words, if I want to make my microbiome healthier, it sounds like I don't have to try and flush all the current microbiota out of there first, is that correct? - Yeah, it's a very good question, and I don't mean to suggest that those things are known to be terrible. Or I would just say, the studies haven't been done. And to me, wiping out this microbial community, unless it's done with some sort of... Unless it's done in an informed way, and we don't really have the information for how that would be done. It just seems like playing the lottery a little bit. - Okay. - And so I think... I don't want to say that those are... It may be that when the study is done, those are shown to be amazing, but I just don't think we have the data to know that yet. So it's somewhat of an arbitrary thing. If somebody out there feels way better when they do this, and are not experiencing problems with it, then maybe it's the right thing for them. But I certainly can't say that it's something great to do. I can't imagine a future where as the microbiome gets incorporated into this emerging paradigm of precision health, you go into a clinic, somebody types your microbiome and says, oh,

there's this huge, massive misconfiguration. You have all these engrafted bacteria that are residents in your gut microbiome that are sending out molecules that are not good for your health. It would be good if we do a mass-reprogramming of it. The way that we do that is we flush your gut, and we actually give a light antibiotic treatment to try to kill everything that's there. And then we repopulate with this other consortium of microbes that we've studied and know are healthy, know are compatible with your human genome, and can be reinforced with a diet that we know is good for you. We'll install those microbes, we'll help you along in the diet so you know how to nourish those microbes, and that will be the way that will reconfigure your gut microbiome. So I can't imagine a future where that sort of flushing,

01:14:50 Your Microbiome & Your Immune System

or cleansing is part of something for repopulating the gut. But right now it seems a little half-baked to me. Yeah. - Great. I'd love to talk about fiber and fermented foods, because you and Chris had a really, what I think is a really interesting and exciting paper at the end of last year about comparing the inflammatome, so inflammatory markers of people who ate a certain amount of fiber, or a certain amount of these fermented foods. This study is amazing for several reasons, but almost as amazing as how diverse the interpretation of this study was in the media. If ever there was a study that was kind of hijacked by different priority schemes out there- - Yeah. - It's this study. So you performed the study with Chris, and your postdocs, and graduate students and staff. What are the major conclusions and what sorts of directives, if any, emerged from this study? And I'll just preface this again by saying, if I wasn't clear, some news report said, "Ah, this means fiber is not important." - Yeah. - And then others said, this means fermented foods and fiber are important. And others said, fermented foods are the thing, and the only thing. It was all over the place. - Yep. - And one of the reasons for doing this podcast at all is so that we can go straight to the people who perform the work. - Fantastic. - And even though I'm certainly not an expert in microbiome, to give you the opportunity to share with me, and me to ask the kinds of questions that have... I have zero agenda. I do like sauerkraut, I do drink the occasional kombucha. I do like low sugar, not so sweet forms of fermented foods. So I would be delighted if fermented foods are good for me, but I have no stake in the fermented and food industry. - Yeah, absolutely. - Yeah. - Yeah, yeah. Great. Yeah, wonderful, and an important note there is

the one you pointed out, that this is an incredible collaboration with Christopher Gardner's lab, and a bunch of people. Erica Sonnenburg helped lead this study, and then tons of, like you were saying, postdoc staff and other people at Stanford, and then wonderful participants that were part of this study. So a huge team effort. Let me tell you, before I dive into that study, let me take a step back, because I think the reason that we did this study, and kind of Christopher's group, and our group has started to pursue this line of looking at dietary interventions and how they impact our microbiome, how they impact human biology, goes back to this kind of epiphany that we we had while studying the gut microbiome. Because I think when we started studying it at Stanford, we were thinking about it as this kind of newly appreciated aspect of our biology, almost like finding an organ that we didn't know was there, and starting to think about like all the drug targets that were there. Can we go in with small molecule drugs, and think of ways to manipulate this community to ameliorate disease? And this is largely the mindset of Western medicine, and largely born out of the era of infectious disease. You wait for an infection to start a bacterial infection, you treat with antibiotics, and that's the way medicine is practiced, and that's become less successful over time, as we've moved into this era of inflammatory, Western diseases, and with the exception of the current pandemic that's sweeping the world, largely moved out of the era of infectious diseases, at least infectious bacterial diseases, that this paradigm of waiting for diseases to appear, and come into the clinic is not really very effective in the context of inflammatory, Western diseases, autoimmune diseases, metabolic syndrome, heart diseases, and inflammatory disease. The list goes on and on. And so we started to think a lot about like, how can we get out in front of this? How can we think about preventative ways of dealing with this crisis of metabolic and inflammatory diseases? And this tremendous, beautiful body of literature started to come forward in the field about 10 years ago that showed that the gut microbiome is absolutely critical to modulating our immune status. So if you change the microbiome, you can fundamentally change how the immune system operates. And we know that the immune system is at the basis of a lot of these disease, inflammatory, chronic diseases. And so it brought up this possibility that maybe the fact that we're not nourishing this community well enough, maybe the fact that it's deteriorated over time due to all of the things that go along with an industrialized lifestyle, antibiotics and so forth. Maybe we have a microbiome right now in the industrialized world that is setting our immune system at a set point, simmering inflammation that's driving us towards these inflammatory diseases. And wouldn't it be

wonderful if we could figure out how to use diet specifically, but just kind of learn the rules of how to reconfigure both the composition and function of our gut microbiome, so that inflammation was different in our bodies, so that each one of us was less likely to go on and to develop an inflammatory disease, leading to better longevity and health over the course of our life.

01:20:17 Dietary Fiber & Fermented Foods

And so we were studying this in actually in mouse models, and realizing that we really needed to start doing human studies. We needed to start studying microbiome in humans, and because we were studying diet, we knew that this was something we could go in and do right away. We didn't have to apply for FDA approval for a drug before we could do a human study, we could just start doing human dietary interventions, longitudinally monitoring the immune system, and the microbiome, and starting to put the pieces together of what is it in diet that can change our microbiome in a healthy way, help us define what a healthy microbiome is, and monitor the immune system in great detail. And so there were really two critical components of this, in addition to our microbiome expertise. One was Christopher Gardner's group. We wanted to do these human studies, but we're absolutely terrified of humans. We work with mice. Humans are terrifying in many ways. - But they house themselves, you don't have to pay- - That's true. - You don't have to pay for their housing. - That's true. - For those that can afford housing, of course, yeah. - Yeah, sadly, just for that portion of the population. So Christopher's group were, they were our masters at working with human populations. And then the other wonderful thing that we have at Stanford is this Human Immune Monitoring Center run by Mark Davis and Holden Maecker. They started this beautiful center for allowing people to do immunology in humans. Critical element, because a lot of the mouse studies don't translate well to humans. So if you can do the studies in humans, similar to how we were thinking about the microbiome, you learn something that you know is relevant to humans. And so having that immune profiling capability where we can monitor hundreds to thousands of different parameters in the immune system, longitudinally in people, from a blood draw, and not just know if CRP goes up or if interleukin-6 goes up or down, but to be able to see all these facets of the immune system change in concert, as we're changing the microbiome with diet was really a key component of this. And so our flagship study, supported by wonderful donors. So this

actually isn't funded by typical foundations and national institutes of health, it was funded by philanthropy. We wanted to understand if we put people on a high fiber diet, how would that affect their microbiome immune system? And if we put them on a high food diet, a diet rich in live microbes and all the metabolites that are present from fermentation and foods, how would that change microbiome in immune system? - Could you give us some examples of what those diets look like? And were you changing their basal diet, or were you just adding things on top of what they were already eating? 'Cause it's hard to change people's diets. - It's very hard. - And then you have to trust that they actually do it and they're not sneaking, and- - Totally, yeah. We started this center for human microbiome studies at Stanford for doing a lot of these studies, and a portion of the studies, we do focus on supplements, probiotics, microbes delivered in pill form. Prebiotics, which are purified forms of fiber. And in those cases, we actually can have placebo groups, because it's more like a drug study, and we don't change people's diets. So we can just administer this on top of what they're doing. So in a way, they're a lot more controlled, but it's not food. When you start doing food studies, you can't do a placebo group, 'cause people know what they're eating. And the other problem is that it's really hard to just change one thing, because as soon as you start adding something, people usually eliminate something else. So the idea was to basically give these people simple instructions for in the case of the high fiber diet, just increasing plant-based fiber. So can you eat more whole grains, more legumes, more vegetables, nuts, get the fiber up in the range of, from 15 to 20 grams per day, up to over 40 grams per day. So can you double or more the amount of fiber that you eat per day, knowing that that would have a tremendous impact on a lot of other facets of their diet. They eat less meat, animal-based protein, less animal-based fats as a product of this. I will say that getting back to Christopher's rule for a healthy diet, a lot of the macro nutrient changes that we saw in their diet were consistent with healthy changes in diet. Less saturated fat, less animal-based protein, more plant-based protein. So a lot of changes that are known to be beneficial came in concert with just telling people, eat a high fiber diet, high plant-based fiber diet. The people that were eating the high fermented food diet, they were instructed to basically eat foods that you could buy at a grocery store that were naturally fermented and contain live microbes. And so this largely consisted of yogurt, kefir, sauerkraut, kimchi, some fermented vegetables, brined, fermented vegetables. - Pickles. - Pickles, things like that. One of the things that I think is a pitfall in choosing fermented foods is, you can go down the canned food aisle and there's this huge section of pickles,

and jars that are canned. Those are not fermented foods. Those are are cucumbers that they've put in a acidic acid and vinegar to reconstitute that fermented flavor, but there's no live microbes involved in that. And even sauerkrauts in the canned food aisle, even if they were naturally fermented, quite often they're not. Quite often they're just brined in vinegar. But even if they are naturally fermented, all the microbes are killed prior to canning or during the process of canning. So what we use for this study and if you want to have live fermented foods that contain live microbes, you need to buy those out of the refrigerated section, essentially. - And I'm really glad you pointed this out, because you can find sauerkraut on the non-refrigerated shelf, that is indeed non fermented. A lot of fermented that are available in the US can be high in sugar. So was there any instruction as to getting people to make sure that they were consuming yogurts that weren't loaded with sugar? - Yep. - Or did you let them just select for the stuff in the cold section that is fermented? - No, super important point. We instructed people to eat non-sweetened yogurts. I think a huge pitfall in this area is you can have a yogurt loaded with bacteria, kind of the base of what's healthy, and then a ton of like artificial flavoring and sugar loaded on top of that. Manufacturers put a ton of sugar in after the fact to kind of mask the sour taste fermented foods, which is hard for some people to become accustomed to. When we were switching to more fermented foods, our daughters were young at that point, we would take plain yogurt, which they didn't like just neat, we would mix in a little maple syrup or honey, just a little bit, and gradually we would reduced that over time to the point where they're pallet adjusted, and now they just really like plain yogurt. But it is, I think, getting used to that sour flavor is difficult, but people really should try to stay away from those fermented foods that are loaded with sugar. And that's what we instructed people in this study. - And beer was not included. - Right. - The number of people that asked, when I did a brief thing on social media about this study, and hopefully I got it right. I think I did. But people just ask about beer. I'm not a drinker, so for me, beer has no appeal anyway. But beer is fermented, correct? But were they instructed to avoid beer or to drink beer? - Just to go with their normal dietary habits, but that did not count as a fermented food. - And kombucha was, as I recall- - Kombucha was, and kombucha can have small amounts of alcohol in it. Yeah, kombucha actually was one of the major things that people drank during, or consumed during the fermented food phase. And the deal with beer is that there may be beneficial properties of the microbial communities in naturally fermented beer, but most of the beer that we buy, again, is canned and filtered, and there's no live microbes there. So very different than if

you siphon it off of your home brew and drink it, probably, than if you buy it in a store. - I will get to the results of the study in just one moment. But I want to say, a lot of people shy away from the high quality fermented foods, because they can be quite costly. And I'll just refer people to a resource in Tim Ferriss's book, "The 4-Hour Chef," he actually gives an excellent recipe for making your own sauerkraut, which basically involves cabbage and water and salt, but you have to do it properly, because you can grow some, not necessarily lethal, but some somewhat dangerous bacteria if you don't scrape off the top layer properly, but he gives beautiful instructions for how to do this in vats. We've started doing this at home now, actually, is we got a, just ceramic vat. And you can make large amounts of truly fermented sauerkraut just from cabbage water and salt, if you're willing to follow the protocol. And if you're interested in science, that protocol looks a lot like what you'll do for most of your graduate career, except maybe some sequencing too. So anyway, just to refer people to a source that's very low cost. - Yeah. - Compared to buying the high quality, fermented foods. Even kombuchas, for some people, it's like $5 a bottle- - Totally. - Only this much. And if you consume liquids the way I consume them, that's just the the start, so- - Yeah. But if you can get your hands on a SCOBY, kombucha is another one that's super simple. - You can grow your own. - You can just make your own, and it's super easy to do. I make it, I constantly have a batch of kombucha going at home. It's a SCOBY, a symbiotic community of bacteria and yeast. You brew tea, you add sugar to it, and you put the SCOBY in, and you wait a week or two, depending upon the temperature, and then you just move the SCOBY or over to a new batch, and you your old, what the SCOBY was in is kombucha, and it's wonderful. - I love it, I would love it if members of this audience would start to make their own kombucha and sauerkraut. I've been having so much fun. I don't do it, but it's done in our home. I don't go anywhere near the food production, and it's for everyone's benefit. So how much fermented food were they consuming? 'Cause you mentioned the number of grams approximately of fiber, but was it in servings, ounces? How many times a day? Early day, late day? - Right, yeah. So we had a wonderful dietician instructing people for this, and her name's Dalia Perelman, and she really was the key and is the key for many of our studies for getting people to eat differently. And the general instructions were for people to eat as much fermented foods as possible, more is better. And the reason is that with this initial study, we really wanted to maximize our chance of seeing a signal if there was something biological going on, with the idea that if the dose was excessive and not easily achievable by a lot of people in the end, we can go back

and and say, okay, this is the point at which we lose the biological signal. But people during the height of the intervention phase, the intervention phase was six weeks, during the height of that, were up over six servings, on average, per day of fermented foods. So kind of two servings at each meal. And the ounces or weight or size, it really depended on what the fermented food was. And we just told them to stick to what was a recommended dose on the package that they were buying, For kombucha, it'd be like a six to eight ounce glass. Sauerkraut like a half cup, or something like that,

01:32:13 High-Fiber vs. High-Fermented Diet; Inflammation

and same with yogurt. - Great. So what were the results? - Yeah, so the results astounded us in a way, but then thinking more deeply, and it'll be evident even after I explain it in the context of this conversation, likely why we saw the results we saw. The results were astounding because our hypothesis going into this was that the high fiber diet was going to give the massive signal. We know that this is the big deficiency in the Western diet. All the mouse studies have told us that high fiber really leads to a much healthier microbiota, it can lead to positive changes in the immune system. And in fact, even when we had a limited... We had wonderful donor support, but still a limited amount of money when we started this study. My lab was really very eager to do the high fiber part of this really well, and Christopher kind of had to twist our arms to do the fermented food side of it. And we thought it was kind of quirky and neat, live microbes should be exciting, let's try it. So we put that in and it turns out that we were very thankful that he twisted our arms, because it was that high fermented food arm that really gave us the big signal. Even though our hypothesis was that the high fiber was going to lead to more short-chain fatty acids produced in the gut, more diverse microbiota, less inflammation in the immune system, we didn't see that across the cohort. We actually saw very individualized responses to the dietary fiber, and I'll come back to what those responses were. The big signal really was in the fermented food group. We saw all the things that you would hope to see in a Western microbiota in western human. We saw this increase in microbiota diversity over the course of the six weeks while they were consuming the fermented foods. And we can't always say that higher diversity is better when it comes to our microbial communities. We know there are cases for instance, bacterial vaginosis, where higher diversity is actually indicative of a disease state, but we know in the context of the gut, and for people living in the industrialized world, higher diversity is

generally better. We know that there's a spectrum of diversity. People with higher diversity generally are healthier. If you can push your diversity higher, you're in better shape. And so we saw that increase in diversity. And then the major question is, what happened to the immune system as these people were increasing their gut microbiota diversity through the fermented foods? So we did this massive immune profiling, and we see a couple dozen immune markers, inflammatory markers decrease over the course of the study. So we measured these at multiple time points throughout the course of the study, and there's kind of this set stepwise reduction in things like interleukin-6, and interleukin-12, a variety of famous inflammatory mediators. And then even if you go into the immune cells and you start looking at their signaling cascades, we see that those signaling cascades are less activated at the end of the study compared to the beginning of the study, indicating in attenuation of inflammation. So kind of exactly what we would hypothesize would lead to less propensity for inflammatory disease over time. That's a huge extension of a very short study and- - How long was this study again? - So the complete protocol I think was 14 to 17 weeks, or something like that. The actual intervention phase consisted of a four week ramp and then a six week maintenance period. So the intervention itself was 10 weeks, but there were six weeks of really kind of hardcore, high levels of fiber or fermented foods. - Yeah, and I'm glad you mentioned the ramp, 'cause my experience with fermented foods is that you, it can be beneficial to give the system an opportunity to act acclimate. I mean, if you consume a giant bowl of sauerkraut, it's not going to be the worst day and night of your life, but you'll know you did. - Totally. - We'll just leave it at that. And so you want to kind of acclimate to it. - Absolutely. - I'm at the point now where, some people might think this is gross, but after I exercise, I've been sweating a lot, I like the saltiness of the... I actually drink the liquid that the sauerkraut has been stewing in, and I get, I like to think that I consume some fermentation that way, it's salty, it as kind of a post-training replenishment. But if I had done that six months ago, straight off, I think it would've been pretty rough on my system. I started taking little bits of it and then adding it each day. - Totally, and so both with the fermented foods and the fiber, it's well known that this kind of gradual ramping is a really important way of mitigating bloating, and other digestive discomfort that can happen when your microbiome reconfigures and starts fermenting more, and changing community members. So you should take that ramp at your own pace. If something seems to be going wrong, just kind of level off, stay there. We did this in a very delicate way to get people up to the high dose. The brine, just a tangent here for a second, that

was actually one of the products that we had people use in the fermented food phase. There's actually a product called Gut Shots, which is just bring that they've marketed. We actually are now studying it in the lab. I just actually, before this came from a lab meeting where a GI fellow in my lab is actually putting Gut Shots, sterilized gut microbe, or the fermentation microbes removed or present into mice and looking at changes in their mucosal immune system. So we're studying this in detail now, because it's a rich source of lactate and a bunch of other interesting metabolites. - I love that my weird behavior is inadvertently being studied at Stanford Medicine. I want to just mention something about the Gut Shots. Those are sold as a drink. Those also, just for certain listeners in different budgets, they can be very expensive if you really think about... Some of them are exceedingly expensive. But what I described before with making your own kombuchas, it's not quite brining, but the homemade sour sauerkraut, that protocol is out there, as I mentioned in Tim's book, "The 4-Hour Chef." And you get a lot of the brining from that, an almost endless amount. A cautionary note, I once went into the refrigerator and saw something similar to Gut Shot, it wasn't Gut Shot. And I drank the whole 12 ounce bottle, and realized that it was 24 servings. And that's where I got my initial experience with what it is to not do a ramp up phase. - Yeah. I do not recommend doing that. Some of these, it's very potent, it seems, and you can consume even a half an ounce or an ounce. - Yeah, I mean, very potent from the standpoint of fermentation, but also very salty. So there's a lot of effects that can.... Yeah. - Yeah, don't do what I do, - Yeah. - At least not at the outset. So that is an experienced warning. So they did this, as I recall, there was a swap condition or there was a halt condition. So you did controls, right? It wasn't just comparing groups. You had individuals in who were initially in one group or the other moved to a different group, correct? Or to stop and then return. - Yeah, we actually just did a stop and followed them during a washout phase. And the ideal situation for dietary interventions like this are to do crossover studies, as you're suggesting. We've recently completed a ketogenic versus Mediterranean diet intervention- - Are those data published yet? - Not yet, but Christopher's been Tweeting a lot of these data and there's a paper in revision right now. So if you go to Christopher Gardner's Twitter feed, you'll be able to find him reporting some of the early results of this study. - Can you give us a snippet of, was there a superior... Just give us a, you don't have to tell us which one, but was there a superior condition of either Mediterranean versus ketogenic? - So the metabolic effects of these, it's a beautiful study. I should let his group comment on that. The microbiota data we actually are just

generating now. So the study that his group has put together from this is largely independent of the microbiota data. - Right. - And now we're doing a more in depth analysis, and I'll have more to say about that the future. - We'll return to that, yeah. - But it's a super exciting study, because it is one of these where people eat a certain way. And what's really beautiful about this is we even got food delivered for part of the intervention. So we had complete control over what they at least had available to eat. And then the second phase, they make the food on their own. And then we cross over and do the same thing. And so that's really like, if you have a good enough budget, the right way to do a study like this. For this, we didn't have the time or money to do a crossover, but we did do a washout phase where people, we didn't make them stop eating, whatever, if they were enjoying it, but we monitored. And there was some recidivism where there was a decrease in fiber fermented food. And we could see, for instance, diversity start to plateau and reverse in many of these people. So there does appear to be a need for maintenance of the intervention to maintain the perceived health benefits that we were measuring. - Great. We will provide a link to the study in the caption, and thank you for that very clear and thorough description, from one of the investigators involved in the study.

01:41:33 Ripple Effects of a Healthy Diet

It's great to go direct to the source. Anecdotally, were there movements in mood, in resistance to colds and infection during the course of the study? And this is kind of a prelude to where I'm headed next, which is there is a tremendous amount of interest in the so-called gut-brain axis. But also I want to make sure that we talk about how these microbes and the conditions they're establishing in the gut are creating positive or negative health effects. I mean, basically how signals get out of the gut. - Totally. Yeah. - So I certainly notice that when I'm eating more fermented foods, or there's probiotics in drinks I consume and so forth, that I feel quote, unquote, air quotes, completely subjective, I feel better. - Yeah. - I wish there was an objective measure of feeling better. But I seem to think more clearly, sleep better, mood, et cetera, and I know I'm not alone in that. And any time I've taken harsh antibiotics, I feel worse, but then again, I'm usually taking them because I'm feeling bad about something else, right? I don't take them just because. So did people say they were feeling better in any way? And if so, what did you have observe? And again, we're highlighting these as anecdata. - Yeah, totally. We, as

part of this effort to look at how dietary interventions affect our health and wellbeing, and so forth, and microbiome immune system, we interact with a lot of people who have read our book, or kind of have become microbiome enthusiasts. And have implemented a lot of these changes in their personal life. And I hear the same thing that you're saying, Andrew, that tons of people say they have more energy. They think more clearly, they sleep better, their family is nicer to each other, like the number of crazy things. And it's really hard to uncouple, like, is this because these people have taken charge now of what they're eating and just feel better in general for being in control of what they're doing, or is there this cascading set of effects that are actually impacting our... Kind of emanating from the gut-brain axis. And so we actually implemented a bunch of questionnaires and even a cognitive test to try to get at some of this. And I should say, the list of this goes on and on. There are people who claim that their complexion improves, and that their allergies... And there's probably all sorts of ripple effects. If you can affect your inflammation, we know that you can affect your cognition, we know that you can affect your skin and inflammation that's occurring on your skin. So I really think that there is a basis for a lot of those anecdotes. It may just be hard to see in a short study and in a small cohort of people over a short period of time, but we didn't really see significant things associated with cognition and moods and all of the things that we were testing for which, yeah, there could be a variety of explanations for that. We also have a standardized stool measure that people use, and there was less constipation, better bowel movements over the course of both of these interventions. So it did seem like bowel habits improved, which a lot of times can lead to better moods, but that we weren't able to measure. - That the classic psychoanalyst would have a few field day with that. What sorts of interesting things did you observe

01:45:00 Does a High-Fiber Diet Make Inflammation Worse?

in the fiber group? Because it's clear that that group yielded some unexpected findings in both directions. Things you expected to see, you didn't see to the same amplitude as you did in the fermented food group, but I'm guessing you also saw some very interesting things in the fiber group. - Totally, yeah. So we started looking at the data in more detail when we didn't see the cohort-wide response. And one of the things we observed is that in measuring all these immune parameters, there appeared to be three different groups of immune responses that we were seeing. One group that got overall

less inflammatory, and then two other groups that kind of had a mixed result, partly more inflammatory, partly less inflammatory in all these markers that we were looking at. And when we started digging into like, what aspect of the biology of those people dictated or predicted which group they fell into, the really interesting part is the people with highest diversity gut microbiomes to start the study were the ones that were most likely to have the decreases in inflammation. And so data seemed to be telling us that if you start off with a diverse microbiota, maybe one that's better equipped to degrade a wide variety of dietary fiber, you're more likely to respond positively to it. If you have a very depleted gut microbiome, you're not as likely to be able to respond to it. And thinking back to that experiment that we talked about before with the multi-generational loss of fiber-fermenting microbes in mice that were fed a Western diet, it may be that many of us in the industrialized world have a microbiome that's so depleted now, that even if we consume a high fiber diet, at least for a short period of time, we don't have the right microbes in our gut to degrade that fiber. And this has actually been observed by other groups, beautiful study out of University of Minnesota, looking at immigrants, coming to the United States. And within nine months, but certainly over the course of years, immigrants that come here lose a lot of the diversity in their gut microbiome, but a lot of the fiber-degrading capacity in their gut microbiome too. So it could be that over time, this becomes a one way street, and it's hard for us to recover microbes that actually can degrade the fiber.

01:47:22 Over Sterilized Environments

And I think that this probably intersects with sanitation in our environment, and the fact that we don't have access to new microbes that might help us degrade the fiber. That we actually have lost these microbes, and they're in some ways irrecoverable without deliberate reintroduction of fiber-degrading microbes. - I can recall from childhood, there were kids that would eat dirt. - Yeah. - And snails and stuff. That just sounds totally disgusting, bu kids covered with mud maybe not so much anymore. And certainly during the pandemic, there's been and a lot more use of these hand sanitizers, that prior to that, people seemed pretty spooked about, but then obviously they prioritized them. Well, you have children. Do you encourage them to... When they were young, did you encourage them to interact with pets and dirt and- - Absolutely, yeah. - Stuff in the environment, provided that stuff wasn't immediately toxic? - Exactly. So this is really... It's a continual

cost-benefit analysis, I think. I will say that with the pandemic now, and certainly just with infectious diseases in general, it's really important to be aware of the possibility for compromising your health through the spread of germs. And so that is just, hand washing is important, and we have to be careful with the spread of germs. But I do think that the sanitization of our environment has gone overboard with various things being impregnated with antibiotics, shopping carts and things like that, and toothbrushes. It's like antibiotics and things for killing microbes are everywhere. And when we were raising... When our daughters were young and we were making these decisions, the calculations that we would make were really one, how likely are they to encounter a disease-causing microbe? If we've been out on a hike or in our garden, just kind of working in the dirt or whatever, maybe it's not as important to wash your hands before you have lunch, even if there's a little bit of dirt on them. If they've been in a public playground where maybe other kids with germs, or maybe even chemicals like pesticides and herbicides that are being used, maybe it's more important than to wash your hands. Certainly if you've been in the grocery store or on the subway, probably a good idea to wash your hands. So I think you really need to think about kind of the context of it. Exposure to microbes from the environment is likely an important part of educating our immune system, and keeping the proper balance in our immune system. And it's just a matter of figuring out the right way to do that safely. And it may be the fermented food result that we saw is a way of tapping into those same pathways,

01:50:15 The Gut Microbiome’s Effect on Physiology

kind of an environmental exposure to microbes that's safe. - Interesting. I'd like to touch on how signals get from the gut to the rest of the body. And we probably don't have time to go into all the systems that benefit from having a diverse microbiome or healthy microbiome. But we talked about the immune system. There's active signaling and transport from the gut, all along its length, as far as I know, into the bloodstream, into other organs and tissues. So for the immune system, it seems straightforward. It could reduce the amount or number of inflammatory cytokines, like IL-6 and so forth, maybe increase the anti-inflammatory cytokines, like IL-10 and others. But we know there's a gut-brain access of neurons that literally talk in both directions between brain and gut. But let's say I'm eating my fermented foods, I'm doing all the right things, and my gut is diverse and I have all the goodies at all the right places. How is it that fact that those

microbiota are thriving is conveyed to the rest of the body? Because they're in there doing their thing, and I don't know that they have a mind, but they're probably not thinking of taking care of me, Andrew. But I feel better, or I might get sick less often, or combat any illness more quickly. How is that actually happening? Is it that the microbiomes stay restricted to the gut, but the signaling molecules are all downstream, in a downstream way, are making good or bad things happen? Or is there some sort of direct recognition at the body level, or are there cells in the body that are responding to, ah, the gut microbiome is healthy, and therefore I can make more of the good stuff, and less of the bad stuff, so to speak. - Yeah, great. You're right, it's super complex. There's a huge array of ways that our body perceives both the microbes and the molecules that they produce in our gut, and the molecules they produce are, of course, a product of what microbes are there, and then what they receive as kind of metabolic inputs, what we're eating and what other microbes are present in the environment, providing molecules to them. So, it's this complex matrix, but we... Probably the simplest place to start is just the immune system. We have an immune system that, the vast majority of immune cells in our body are located in our gut, just because there's such a dense population of microbes there that have... We consider them beneficial microbes, but they're only beneficial if they're in the right spot in the gut. As soon as they mislocalize, we know that they can become opportunistic pathogens. And so the immune system really playing an important role to keep with them in place is essential for this system not moving into a disease space. The immune system has a variety of ways of monitoring what microbes are there. They're actually specialized to structures in the gut known as peyer's patches that actually take up microbes. They actually allow microbes to transit into this population of immune cells in a very controlled way, so that that set of immune cells becomes educated as to what microbes are just on the other side of the barrier. - Wow, kind of like a border patrol. - Exactly, yeah. So they bring them in, they fingerprint them, and then have kind of this set of responses ready to go if needed. - [Andrew Huberman] Amazing. - There are other cells known as dendritic cells, special type types that actually send long arms, these processes out into the lumen of the gut, and do the same thing, take up microbes, bring them back in and sample them. In addition to these direct sampling mechanisms, the cells that line the gut have a huge array of receptors, specialized proteins, that perceive patterns, molecular patterns that the microbes make. So things like endotoxin lipopolysaccharide, just the cell wall of the bacteria. We have specialized receptors that recognize those. If those signals become too profound, or if

they're perceived in the wrong place, that can stimulate an inflammatory response. So there's all these ways of monitoring the membership, and where it is and how close it is. But then there's this whole other set of ways of perceiving metabolic activity, and what's happening in the gut. And you mentioned before, these cell types, that express taste receptors in the gut and have ways of sampling dietary components. They're the same types of, or analogous cells in our gut that are perceiving metabolites produced by the microbiota so that our bodies can perceive what sort of metabolic activity is going on. And then in addition to that, there's this tremendously important nervous system that's sending signals back to the brain, dictating things like motility. Do I get rid of what's in here? Do I move it along quickly? What actually is happening? Do I need to interact with immune cells? So there's this really complex array of interactions between the different cell types. And then a lot of the cells that are in the gut, perceiving all of these signals, a lot of the immune cells can actually get up and leave. They can get into the blood, cycle through, and then home to other regions of the mucosal surfaces, so that mucosal surfaces are educated broadly against what's passing through our gut. So there's a variety of ways of cells communicating, and then a lot of the molecules that the microbiota makes can actually make their way into the bloodstream directly. And so the array of molecules is still being defined, we're trying to figure out what all these chemicals are. We've mentioned the short-chain fatty acids, but those are just the tip of the iceberg. They are really interesting compounds like indole derivatives and phenols, derived from amino acids, metabolized by gut microbes, taken up into the bloodstream. And then we further metabolize these, they become kind of co-microbe host metabolites, and then they can go on and bind to different receptors throughout our body, anywhere our bloodstream has access to,

01:56:45 Gut-Brain Connection

and start to trigger signaling cascades. - Is it known whether or not any of those molecules are small enough to cross the blood-brain barrier? Because the hypothesis it and the current thinking is that neurotransmitters manufactured in the gut, and signaling along the gut-brain axis, literally neurons talking back and forth electrically from brain to gut and gut to brain is what regulates things like mood, or at least in animal models. And there are some emerging human studies, improvement of symptoms in autism spectrum disorders, maybe even in ADHD. What I'm basically saying here is there is some

evidence emerging that improving the gut microbiome can improve outcomes in psychiatric and developmental disorders. But what you're telling me is that the microbiota themselves are manufacturing chemicals that can make into the bloodstream. And therefore I'm asking if those chemicals can move from the bloodstream into the brain directly. It may not be a gut-brain axis via neurons. It actually could just be seepage of serotonin into the brain, or acetylcholine into the brain for that matter. - Totally, yeah. The biology of most of these molecules is not well understood, but certainly in like cerebral spinal fluid that's been analyzed, you can perceive these microbial metabolites, so they are there. - That's the answer, yeah. Some of them are getting across the barrier. - But so a really interesting thing is, I think a lot of these molecules are, if they're experienced at high enough doses, are toxic or have toxic properties. We know that a lot of these metabolites, when they make their way into the bloodstream, eventually are excreted through the kidneys in urine. So actually we can monitor the metabolism that's going on in your gut by actually looking at the metabolites that are present in your urine, because many of those originated in your gut, from your gut microbes. But people with kidney disease, whose kidneys' filtering processes is not functioning properly, actually build up high levels of many of these metabolites into the bloodstream, and that can lead to more of these molecules making it across the blood-brain barrier. And in fact, some of the transporters in the kidney that are responsible for shuttling these molecules out into urine, are also founded the blood-brain barrier for shuttling the molecules back into the bloodstream if they do get across. - Incredible. - And we know that mental fog one of the big symptoms of kidney disease, potentially because a lot of these metabolites accumulate in blood, and then make their way across the blood-brain barrier into, yeah, the central nervous system. - Amazing. I'm glad you mentioned mental fog.

01:59:30 Probiotics: Benefits & Risks

A few years back, there were some reports, some scientific reports and as a consequence in the media, that excessive intake of pill-form probiotics could create mental fog. I don't know if that ever took hold. And it raises a general question about pill form probiotics. I took them for a few years, just thinking that would be good for my gut microbiome, and then I switched to the fermented food thing, largely there's a consequence of the work that you and Chris published. But what what's the thought

about probiotics for the typical person that's not recovering from a round of antibiotics or that has been prescribed them? I've heard that the species of microbiota that they proliferate might not be the species that we want to proliferate, but I've also heard that maybe that doesn't matter. So what's your general stance? They can be quite expensive. - Yeah. - Also, I know I've been talking about expense a lot today, but I always want to take into account that people are showing up to the table with a variety of budgets, and probiotics are one of the more expensive supplements out there. You can quickly get into the several hundreds of dollars per month if you're getting the quote, unquote, best quality ones. - Right. - And if they're actually causing brain fog, then I'm not sure I'd want to use them. - No, completely. And there's a ton of snake oil out there. People know that they... I think many of these companies are aware that they can prey off of people's fears and get a lot of money from them with absolutely no data to back up that their probiotic is doing anything. So I think the first thing to say is buyer beware, because it's a supplement market, it's largely unregulated. And that means that there are a lot of bad products out there, and a lot of products that even though they're not intended to be bad, just don't have great quality control. There have been several studies that have taken off the over the counter, just kind of off the shelf probiotics, surveyed what's in there based on sequencing and shown what is in there does not match what's on the label. - And that's true of many supplements, and unfortunately supplement companies. This is something we get into on the podcast a lot. There are reputable brands and they go through a lot of work to get things right, and there are many that just for whatever reason, it just doesn't match what's listed. - Exactly, and so there are places that probiotic companies can send their product to have it independently validated. So you want to look for that sort of validation on a product. There also are names that are just very well-known, and their reputations are on the line, so they probably invest a little bit more in quality control than maybe some of the other, lesser-known names. But there's a huge range of data on probiotics. And I think, the thing that we kind of recommend is, try to find good products and then experiment for yourself and see if you can find something that works for you. I know people who have experienced constipation and don't want to change their diet, and have found a probiotic that helps them with that. If you can find that right mix, great. That's wonderful. I would say that the data right now is not overwhelmingly positive for what probiotics do to the gut microbiota. So there have been some nice studies looking at the impact of probiotics on recovery after antibiotic treatment. And it appears to slow down the recovery of the

mucosal microbiota. And some other studies that have where the big signal isn't seen, as you might hope, with a probiotic that's supposed to treat a different disease. There have been metaanalysis that do suggest in certain instances, recovery from antibiotics that there, even though it may cause your microbiome to recover more slowly, that it may actually prevent diarrheal disease, recovery from viral diarrheas, probiotics may help. But because there's such a huge range of products, and because each person is their own little caper when it comes to the microbiome, it's really hard to know whether there are great products for a given indication. The really good advice that I've heard is try to find a study that supports in... A really well designed study, and this is very hard for people who aren't scientists to evaluate. But so if you're experiencing a medical problem, or want to consult a doctor, that that might be helpful. But finding a study where a specific probiotic has successfully done whatever it is you're looking for, and then sticking with that probiotic is really the best recipe as a place to start in this space, I think. - And what about prebiotics?

02:04:20 Prebiotics: Essential?

Is there are a number of reasons why, I can imagine, that prebiotics would be beneficial? Which essentially it's, you're pushing the fiber system, which we've talked a lot about today. - Yeah, yeah, absolutely. The studies that have been done on prebiotics, it's really kind of a mixed bag of results. There have been studies done with purified fibers where you actually see micro biodiversity plummet over the course of the study, because you get a very specific bloom in a small number of bacteria that are good at using that one type of fiber. And that's at the expense of all the other microbes that are in the gut. And so it's really hard to replicate with purified fiber what you'd get, for instance, at a salad bar, in terms of the array of complex carbohydrates that you would be exposing your microbiota to. And I think the kind of broad view of this in the field is that consuming a broad variety of plants, and all the diverse fiber that comes with that is probably better in fostering diversity in your microbiota than purified fibers. Now, there are, again, a lot of people who benefit from purified fibers, either for GI motility or for other aspects of GI health, problems that they've been experiencing. Again, I think it's the type of thing where you have to try to find the thing that's right for you. But there also are studies that suggest that if you layer rapidly fermentable fibers on top of a Western diet, you actually can result in weird metabolism happening in your liver, because you have this incredibly

rapid fermentation of fiber along with a lot of fat coming into the system. At least that's the theory. And in a mouse study that was published a few years ago, they actually see that a subset of the mice develop hepatocellular carcinoma when they're fed a high dose prebiotic- - Liver cancer. - Liver cancer, a on top of a Western diet. So whether that's representative of human biology, we don't know, but purified fibers are definitely very different, both in terms of the diversity of structures, but also in terms of how rapidly they're fermented in the gut. Because if you are eating plants, the complex structures there really slow the microbes down in terms of fermentation, and you end up with a slow rate of fermentation over the length of your colon, as opposed to this big burst of fermentation that can happen if you eat something that is highly soluble and easily accessed by the microbes. - Interesting, so I guess,

02:07:00 Tools for Enhancing Your Gut Microbiota

is it fair to come back to this idea? Try and avoid processed foods, the highly palatable foods, they're all sometimes super highly palatable foods. They're now called, that are packed with hidden sugars, emulsifiers. So it sounds like some fiber is good, and despite the outcome of the study, you identified that if you have the appropriate microbiota background, then one will even better to the fiber, maybe a longer ramp up phase for those folks, and then the fermented foods. 'Cause there's no reason why you can't do both. And as we've talked about before, a lot of fermented foods have fiber. So you can kill two birds with one stone. - Totally. And it could be that the diversity increase that we saw in the high fermented food group could be something that would aid the high fiber group. And so now we're planning another study coming up where we're doing high fiber, high fermented food, and then fiber plus fermented food, just to see if there's a synergistic effect there. - Great, I want to enroll, seriously. Although I guess I'm biased, 'cause I was sort of know where you're trying to.. Well, is it blood draws that you use to measure the inflammatome? - Exactly, so we do blood draws- - [Andrew Huberman] Blood draws don't lie, so that's good. - Yep, yep, right. - So you've covered a tremendous amount of information, and I'm incredibly grateful. This was a area of biology, that despite having learned a lot about through papers and going to talks and reading articles in the media has remained somewhat mysterious to me until today. You've given us a very vivid picture of how this system works. Where can people find out more about the work that you're doing? We can certainly provide links, and your wife

who co-run your lab, you have a book on this topic. So could you tell us about the book, where we can learn more about Sonnennburg Lab and the work that you're doing? Maybe people will even try and enroll in some of these studies. - Yeah, fantastic, yeah. It'd be great if we could get people to enroll. We're always looking for willing participants. Yeah, so Erica, my wife and I wrote a book called "The Good Gut," and that really was a response to how we were changing our lives in response to being in the field, being very familiar with the research. Seeing that a lot of our friends that weren't studying that got microbiome, but were very well informed, many of them scientists, were not doing the same things we were doing. And it was very clear that it was just the lack of information funneling out of the field to other people. And so we were wanted to make that accessible to people who are not microbiome scientists. There's also a really interesting story. We were at a conference site that just has scientific conferences all summer long, week after week, after week, different fields. And so it's people that work there that are just dealing with these new groups coming in week after week and the week, we were there for a microbiome conference, people that work in the dining comments came up to us and they said, "What group is this? This is weird." And we're like, "What's weird?" And they said, "We can't keep the salad bar stocked." And it was very clear that nobody was doing what we were doing until we'd go to a microbiome conference and then everybody was doing the same stuff that we were doing. And so anyway, we wrote this book to talk about our personal journey and the science in the field, and yeah, just to lay a foundation for people if they want to start thinking about these changes. And then in terms of connecting with our research, certainly there's the Center for Human Microbiome Studies at Stanford, which is kind of our home base for doing a lot of these dietary and interventions. We list the studies there, give more information on what we're doing. And then we have a lab website too that people can go to and read more about our research. Yeah, and we're always looking for participants for our studies. - Great, well, we will provide links to all of those sources. And I just want to say, thank you so much for sharing with us your knowledge for the incredible work that you and Erica, your wife and Chris do, and are continuing to do. I think this is an area that, when I started my training, I heard a little bit about microbiota, and I always just thought that are people that work on infectious disease and all the bad stuff. So it's interesting and, and really important that people realize that we're carrying all this vital cargo and we need to take care of the cargo so it can take care of us. So thank you so much for your time

02:11:12 Dr. Sonnenburg’s Research, Zero-Cost Support, YouTube, Spotify, Apple Reviews, Sponsors, Patreon, Thorne, Instagram, Twitter, Neural Network Newsletter

and for the work you do, and I hope we can do it again. - Thanks Andrew. This was a great conversation. - Terrific. Thank you for joining me today for my discussion with Dr. Justin Sonnenburg, all about the gut microbiome and how to optimize your gut microbiome for health. Please check out the Sonnenburg Lab webpage, that's Sonnenburg, spelled S-O-N-N-E-N-B-U-R-G-L-A-B .stanford.edu. That's sonnenburglab.stanford.edu. They often recruit for studies exploring how different aspects of nutrition impact the got microbiome, much as we discussed during today's episode. Please also check out the book that he and his wife, Dr. Erica Sonnenburg wrote, called "The Good Gut." It's readily available on all the usual sites, such as Amazon and so forth. If you're learning from and are enjoying this podcast, please subscribe to our YouTube channel. That's a terrific zero-cost way to support us. In addition, please subscribe to the podcast on Apple and Spotify. And on Apple, you have the opportunity to leave us up to a five star review. You can also leave a comment on Apple, if you like. The best place to leave us comments and feedback, however, is on our YouTube channel in the comment section. There you can suggest topics that you'd like us to cover in future episodes, guests that you'd like us to interview, and give us feedback about any of the material that you've heard or watched on this podcast. Please also check out the sponsors mentioned at the beginning of today's episode, that's the best way to support this podcast. We also have a Patreon, it's patreon.com/andrewhuberman, and there you can support the podcast at any level that you like. On many episodes of the Huberman Lab Podcast, including today, we discuss supplements. While supplements are certainly not necessary for everybody, many people derive tremendous benefit from them for things like sleep and focus, and indeed gut microbiome support. The one issue with supplements, however, is that many of the supplement companies out there do not independently test their supplements. So there isn't tremendous confidence in all supplements that they contain the amounts of the ingredients that are listed on the bottle, and that the quality of the ingredients is where it should be. For that reason we've partnered with Thorne, that's Thorne, T-H-O-R-N-E, because Thorne supplements are known to have the very highest levels of stringency with respect to the quality of the supplements and the amounts of the supplements listed on their bottles list what's actually in the containers, which is essential. If you'd like to

see the Thorne supplements that I take, you can go to Thorne, T-H-O-R-N-E, .com/u/huberman, and you can get 20% off any of the Thorne supplements that are listed there. Also, if you navigate deeper into the Thorne site through that portal, thorne.com/u/huberman, you can also get 20% off any of the other supplements that Thorne makes. If you're not already following Huberman Lab on Instagram and Twitter, please do so. There I cover topics about science and science-based tools, some of which overlap with the content of this podcast, much of which is separate and unique from the content of this podcast. We also have a newsletter, it is called The Neural Network Newsletter. Once a month, we put out short summaries of podcast episodes and key takeaways, actionable takeaways in particular. You can sign up for that by going to hubermanlab.com. You can look in the menu, look for Neural Network Newsletter. You can download previous newsletters to take a look at what those are like and about even before signing up. If you subscribe, we don't share your information with anybody. The privacy policy is made very clear at hubermanlab.com. So thank you once again for joining me for today's discussion about the gut microbiome, and last, but certainly not least, thank you for your interest in science.