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 Saunenberg. Dr. Saunenberg 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. Saunenberg 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 premiere 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. Saunenberg co-runs his laboratory with his spouse, Dr. Erica Saunenberg, 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. And today you're going to learn all of that from Dr. Saunenberg. 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 well-being and performance. In addition, I will of course describe tools and actionable items, most of which I have not discussed on the Hubertman Lab podcast or anywhere else. Pre-sale tickets for the two events go live Tuesday, March 8th at 10 a.m. Pacific time. We've made these tickets exclusively available to the listeners of the Hubertman Lab podcast, so they are password protected. To find them, you can go to HubertmanLab.com slash tour and use the code Hubertman. 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 and effort to bring zero cost to consumer information about science and science-related tools to the general public. And now for my discussion with Dr. Justin Sonnenberg. 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. 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 microbiota or got microbiome. And the density of this community is astounding. And the only thing that's 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. And there's a lot more 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. if you start to get to know them and see who they are, break out in the gut probably to hundreds to a thousand 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 bacteria 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 bacteria fages that infect bacterial cells. And those actually outnumber the bacteria like 10 to 1. 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 in 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, 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. So it's a different way of thinking of the human body. Interesting. I believe that our pH, or the the pH of our digestive system varies as you descend, as you go from mouth to, you know, 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 like 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, you know, built to deal with oxygen very well. They're, you know, in an area that is exposed to a lot of oxygen. They, of course, see different nutrients than, for instance, a colonic bacteria would see. And they grow quite often in in mats that live, you know, on teeth. So they're very structured in terms of end and not moving around a lot. So they're very fairly stationary. As you move down the digestive tract, there are microbes in our esophagus and our stomach, but those are, you know, those communities are not very dense and actually not very well studied. We know of a very, you know, there's a very famous stomach, bacteria known as helicobacter pylori, which can cause stomach ulcers and cause gastric cancer in some, some, you know, less frequent situations. But, you know, this is a very different set of microbes. They have to be adapted to a different environment and 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 study, 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 study just because it's the easiest to access 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, you know, 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 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 like land rush for, you know, this open territory. And so the, you know, 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 know, 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, you know, 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, you know, if you step away from that extreme side of things going wrong, there also are 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 your breastfed 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 this is, that the field is playing 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 the, you know, getting back to that original question of where 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, you know, 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 a kid in, 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. Exactly. Yeah. And so the, you know, the best studies that have been done have just looked at pets in the household as a factor, and whether that changes, you know, 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, you know, we, I have a dog, that dog occasionally will lick my mouth without me like paying attention, you know, and that's probably introducing microbes. We also know that, you know, pets are down in the dirt. They're, you know, outside, they're, you know, they're, they're being exposed to a lot of environmental microbes. And so just, you know, pets serving as a conduit for a bunch of microbes that we wouldn't otherwise come in contact with is a possibility as well. Actually, well, we will return to pets in 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 to have an ease, right? Have an ease. What was your dog saying? Louie, Louie, Louie, pastor. Louie, pastor, I don't know how appropriate. Amazing dog, what a personality on the dog. The issue that I think a lot of people are probably wondering is, what is a healthy microbiome? And what is it, what is it supporting? We, we hear that you need a healthy microbiome to support the immune system or metabolism or even the gut brain access. 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 are 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, you know, there are sessions at conferences, there are review articles being commissioned, there are all sorts of kind of thought pieces about this right now, like what is a healthy microbiota? What are the features that define it? And, you know, 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. You know, it's plastic, it changes our human biology, which I think is, you know, how we think about health quite often BMI and, you know, longevity, reproductive success. However you want to define it, it certainly can accommodate a variety of configurations of got microbiota. And we don't have, you know, it's really hard to untangle all of the different factors of what could be, you know, 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 got 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 got microbes. And, you know, it's important to contextualize the amount of information that they're trying to document the collective genome of our got 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, you know, scales by 10 to 100 fold. So really a huge amount of 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 disease 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. And, you know, they, there were some answers from that, but you 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, you know, conclusions 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, you know, 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, you know, I think that's kind of a big question right now. I think, you know, there's a great quote from Dupchansky that says nothing in biology makes sense except in the light of evolution. And, you know, these traditional populations are all modern people living on the planet now, but their lifestyle does represent, you know, the closest approximation to how our ancestors early humans lived. And so those microbiomes, and now we know from sequencing of paleo feces, the microbiome of these traditional populations is representative, more representative of the microbiome that we evolved with, that potentially shaped our human genome. And so one possibility is that in the 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, you know, deteriorating in the face of antibiotic use and all the problems associated with 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 very important thing. And there is a perturbed microbiota that's really predisposing people to a variety of inflammatory and metabolic diseases. It reminds me of the, as a neurobiologist, I 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 you were studying in 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 my, let's say my, let's aim it at me, if my, 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, you know, we refer to as kind of reprogramming the gut microbiome. And, you know, I think if we want to conceptualize humans as this aggregate human microbial biology, you know, 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, you know, genetic engineering for curing disease. But it's much easier to change gut microbes for a problem just because that, that community is, is malleable. The issue that I think we're seeing in the field is that microbiomes quite often, whether they're diseased or healthy existence, 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. Even individuals, for instance, that get antibiotics, you know, you take oral antibiotics, the community takes this huge hit. We know that a bunch of microbes die, the composition changes, and you know, 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 this, it's almost like a memory where it snaps back to this something that's very similar to the original state, even though the diet remains different. And so there's this incredible result 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, you know, 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 you know, one of the really kind of simplest and nicest examples of this is an experiment that we performed with mice where we, you know, 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, you know, if you switched to kind of a Western-like diet, a low fiber or higher fat diet, what happens to the gut microbiota? And we saw the microbiota change at 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, you know, as fairly, you know, 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 a low fiber or high fat diet and then kept them on that for multiple generations, we saw this progressive deterioration over the course of generations where by the fourth generation, the gut microbiome was a, you know, a fraction of what it 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 it was, you know, so you're 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 virus. It's a combination of access to the right 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. Exactly. Which generally is true of human behavior too, although it depends. And we can all do better nonetheless. Very interesting. A puzzle, a bit of a conundrum around this notion of species of microbiota. So if the pH, if the acidity is differs along the digestive tract, but is more or less fixed for a given location. I mean, less something is really off the pH of the stomach is within a particular range and the intestine and so forth. And certain microbiota thrive at a given station, a given location along the digestive tract. And the pH is 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? If 30% of a fecal matter is microbiota, then where are they living? Are they along the lining and the little microbioli 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? And 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? Who are they attaching to? What are they talking about? What are they doing for fun? And so forth. Yeah, super, super interesting. So I'll come back to the attachment question and kind of like why they don't get washed out because this is super fascinating question. And I think your initial point of like the kind of regional differences and 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 by carbonate 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 and there are bile 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, you know, its purpose is mainly absorbative. And so there has to be flow of a lot of things, you know, a lot of nutrients from the luminal contents into host cells. 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, you know, 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, you know, 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 absorbed to 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, you know, 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 bacteria and letting small things like nutrients. And 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'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, you know, these bacteria like acrimansia, mucinifola, mucus loving, it's one of its main things it does is actually eat mucus in the gut. That's its lifestyle. And so there's, you know, 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 that pithelium. And there are microbial communities that conform 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 for resisting getting washed out 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. 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 I certainly exist out there. What's the idea about cleanses and fasting as it relates to the health or the dysbiosis of the microbiota? 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. 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 are so many diseases that we're dealing with metabolic syndrome and flammatory 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. Things like fasting and a lot of other therapies that have been developed in the field, I think ketogenic diet may be kind of 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 reasons for the popularity of intermittent fasting, time restricted feeding, and sort of what do they call them now, exclusion diets where you entirely exclude meat or you entirely exclude plants or whatever it is that adherence is sometimes easier in the all or none. As neurobiologists, we think of this as a go-no-go circuitry. It's harder to make decisions, nuance decisions often about food than it is to just eliminate entire categories of food, not eating for many people is easier than eating smaller portions. Yeah, and 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, you know, I think that to kind of slice through the nuance of all this, there's a very simple recipe and a really well accepted kind of broad definition of what a healthy diet is. The Mediterranean diet plant based diet is, you know, there's just a ton of data that particularly people of European ancestry, but there's a, you know, a pretty broad acceptance that if you eat mostly plants for most people that's going to be very healthy to the point where, you know, 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 dietitian who was trying to get all the rules of like 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, you know, 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, you know, 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 should I just eat a ton of whole plant, you know, whole grains, legumes, vegetables, fruit that's high fiber-based, not high sugar. Did you completely exclude meat and fish and dairy? And he was saying like, you know, people can add their own spins on this, but I think that the main rule is just start off with, you know, and it kind of gets back to Michael Pollan's mantra. You know, eat food not too much mostly plants. I think if you stick with kind of these simple rules and don't overthink like, should I have this, you know, can I eat eggs, can I eat, you know, just kind of stick to these simple rules, it makes it very approachable. But I agree, like, 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, it's really well known. And they just said, well, it's really hard to get people to change their diet unless you're doing either a go-no-go sort of thing like, or eliminating something. So, you know, 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. So, I think that, you know, we, when we're thinking about things like fasting and, you know, 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 dated it back it up. The, you know, the data in the field really shows that with like fasting, particularly if you go to like animals that hibernate or things like that where there's really extended fast, 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, you know, bacteria 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, it seems like the, you know, 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, so fasting short term might be fine. Probably, you know, 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, you know, the cleanses and the flushes and all this. Personally, I think it's a terrible idea. I mean, we know that like, if, you know, and 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 the, the 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, you know, what microbes are going to colonize who's going to take up space after you do this flush or cleanse. And, you know, that I think it's a little bit like playing Russian roulette. You may end up with a good microbial community in their 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 slash time restricted feeing seems to be getting some traction in part because at some level, we are all doing this when we sleep. But most of us are needing 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 follow that regimen or aid time restricted feeding regimen, but also some who's all the more traditional meal spacing as well. Of course, the one of the things that I wonder about as we talk about primarily plant based with some, you know, what did you say the pollen thing was it was a mostly plants and then maybe some meat but not too much or not too much food mostly plants not too much. Got it. Sorry. Eat food not too much mostly plants. Got it. You know, and in just I hear this again again. I know there are a number of people who do seem to do well on a lower carbohydrate. You know, even some people who report feeling much better on a like really strictly almost meat organ only diet and the only reason I raise this is not I don't participate in any other I'm going to 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 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 and. Ancestually protein was more scarce so eggs and meat and things 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. Skin and avian roots or somebody who has South American roots or somebody that descended from a different tribe will do better on one particular diet versus another and. There by where I should say and in parallel with that that they're got 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 great so a few notes the first one has to do with the carbohydrates and restriction of carbohydrates and some people feeling healthier when they cut carbohydrates out my guess is this 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 industrialized countries. The carbohydrates are largely crap process their process there it's like starch simple sugar it's things that contribute to glycemic index it's it's these sugars that that we eat they make it to our small intestine they get chopped up into simple sugars absorbed into our blood stream 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 car 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 that are bad if you consume them in too high quantity things like you know 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 got microbiota can ferment them and so the you know I think I think we probably all would be better off with less of the carbs that were typically served but most of us and probably the vast majority of our carbs are the most of us the vast majority of us would be better off by consuming a lot more carbs that were complex that were microbiota accessible and I'll come back to why that's important in terms of our biology there are 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 is kind of the classic example of this just over the past 10,000 years humans you know 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 humans human genome genetically adapting to diet in a very short period of time and this there are other examples of this and I'm not going to say that for example of this and undoubtedly this has happened throughout the world to various aspects of diet so certainly it's important to remember that there will be different diets better better for different groups based on what genes you harbor and have in your in your human genome the other aspect on top of that is that you know there are good examples of the got 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 this seaweed it has a dietary fiber in it notice porpharin that porpharin will shoot through most of us untransformed inert substance you know it'll do other things like retain water and service 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 consume seaweed eat seaweed they have a gut microbe that can now metabolize porpharin and so there are these very specific gene transfer events where the genes for breaking down porpharin have been imported into the microbiome of many people in Southeast Asia to you know we can think of it as helping digest porpharin but it's really just a microbe that's found in 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 human genetic adaptations and there are microbiome adaptations that are cultural and based on people's geographic location but you know that 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 gathers foraging consuming huge quantities of plant material just because that's that's what was there and so one of the groups that we study the hudza hunter gathers in Africa and I should take a moment just to say that you know 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 you know are 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 you know leading vulnerable existence and so we really take great care in our research program and it's important for people to realize that you know these populations take partner 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 is been gained through their generous contribution to our research program the hudza hunter gathers it's estimated consume on the order of 100 to 150 grams of dietary fiber per day and that's in start contrast to the typical American that consumes about 15 grams so somewhere 7 to 10 full decrease in the main nutrient that feeds our got microbiome in the American diet the the hudza are you know one example there are different many different foraging populations but the vast majority of these populations consume huge amounts of dietary fiber because plants are the reliable consistent source that you know if you as a hunter gather or go on a hunt usually that hunt is unsuccessful you know I think the data that you know one out of 20 to 30 hunts are successful in landing actually big game for the hudza they have you know birds that they shoot and small animals but they're quite often day after day they're relying upon berries tubers beobob fruit you know they're relying on the plants in their environment and actually if you go to the data and look at what their food 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 you know our brains are wired for caloric density and so if you took a hudza and put them in a restaurant in the United States they would make the same crappy decisions that we make because we you know all want sugar and fat and calories it's how our brain is wired and protein and fat are essential for brain development as far as we know right so that so it sounds like the hudza I hope I'm pronouncing that correctly you said would prefer to eat meat and honey but they do they happen to consume a lot of plant fiber as a consequence of what's available the one of the questions I have is it relates to all of this is it 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 or heavily processed foods in general and I mean not that you know the occasional consumption is is necessarily bad but I'm whether or not one is thinking about one macro nutrient profile or another it sounds like consuming process foods is just bad for the microbiome can we say that categorically for sure okay yeah you know so your low-carb person your zero-carb person your 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 is paramount yeah and I think that's completely compatible with what Christopher saying he was saying if you put prioritize getting a huge amount of 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 so 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 what you know 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 you know and again thinking about the spectrum of a plant based diet versus a meat based diet you know there's a lot of data to tell us that 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 to for people to look at and be aware of the plant based diet if you're eating a bunch of complex you know fibers that feed your got microbiota you're got microbiota produces these substances called short-chain fatty acids things like butarate and it's known that these short-chain fatty acids play really essential components both in terms of fueling colonisites enforcing the barrier keeping inflammation low regulating the immune system regulating metabolism and so you know a lot of people think of dietary fiber is this inert substance that passes through makes us 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 got microbiota your got microbiota is just producing this vast array of fermentation and 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 you know something that will spike your insulin and you know 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 rules so so just to to round out that that topic I think there is a reason to think that you know 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 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 you know 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 got microbiome and can lead us towards the end of the week and then we're going to have a lot of the metabolic syndrome actually there's been beautiful work out of the white's minutes to to on this and then emulsifiers these compounds that are put in process foods to help them maintain shelf stability so things don't separate and so you know all the the moisture content is retained appropriately many of these are known to disrupt the mucus layer and as soon as you start the direction of inflammation and in animal models we know that can lead towards metabolic syndrome as well so there's there's components of process food that are when studied in isolation known to have a direct negative impact on got biology and the microbiota they mention of artificial sweeteners is interesting I confess it's a third rail on social talking about artificial sweeteners there 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 judgmental mainly based on the mouse studies and then there 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 in the middle there however 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 from out of Diego Borges lab at Duke University that the neurons that live in the gut mucus of these neuropod cells can actually distinguish between artificial and true sweet sugar versus artificial sweeteners base they send different patterns of neural signals up to the brain and the brain circuitry seems strongly impacted so I think as the data emerge we're hearing more and more of these artificial sweeteners either are problematic or at least are signaling different events in the in the gut I do want to make sure that we distinguish artificial sweeteners from non caloric plant based sweeteners 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 sweeteners into one big category and say 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 ask for a what do we know anything about plant based non caloric sweeteners or low caloric sweeteners very little you know a lot of those have a lot more bang for the buck they're they're incredibly sweet so it takes a really small amount for them to trigger a huge amount of sweetness and 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 very important to the brain and the brain is not going to be able to do that. So I think that's a really good idea to be that those are actually you know 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 you know 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 you know kind of evolutionary exposure to these compounds in our diet historically there are I think traditional populations that use these for instance to sweeteners and that's not going to be the most important thing to do is to get the best out of this. So I think that's a really good idea to have a lot of different populations that use these for instance to sweeten you know sweeten different foods that our bodies just kind of know how to deal with those compounds better than the ones that are synthetic but I think the you know this study still need to be done. Do you actively avoid artificial sweeteners sucriloes as per tame saccharine you personally. Yeah you know so I do I avoid them but I'm not I you know so that you I work closely with my wife Erica as you know we do we run the lab together and we you know 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 and the got microbiota over the past 15 years and you know I think that one of the things that I think that's not going to be the best way to do it is to get the best way to do it. You know I 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 and so so they're very few rules that I have that are hard and fast I'm I'm a pretty flexible eater I don't believe that having an artificial you know having a diet coke will you know 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 I'm not going to do that. I'm not going to do the flavor of them I'm super sensitive to the nuances of the flavor even with the you know stevia and Magro sites from monk fruit and stuff like that I just really the off flavors are really hard for me to deal with. But so so but I also in this journey of changing our diet like when we started off in microbiome research I was in the habit of you know in the afternoons having a sweet a muffin or a cookie or something like that and when we started to realize that we you know we should be eating less sweet since eating more dietary fiber. This was an incredibly difficult change for me to make I was just wired to kind of crave you know this classic scientist. Scientists love the the pastry in the after you know the coffee yeah yeah the old days it used to be a cigarette too right exactly when I started my training a lot of people still smoke yeah right and it was only during my postdoctoral training that they eliminate smoking on campuses and and productivity took a took a trough for a while and until these people developed other tools to focus their attention. Exactly exactly so there is this kind of like need and then once you have an ingrained behavior and maybe things that are addictive it becomes incredibly difficult to break that habit and and so I would say you know gradually over the course of like you know five or more years we have you know migrated our diet away from sweet foods to things that are less sweet. And it's you know 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 palettes and it's amazing how this happens now where I'll have something that you know is something that I would have used to have like daily and it's unpalatable I like I just can't deal with the sweetness of it and and so I avoid I certainly avoid artificial sweeteners but I also avoid just sweet things in general that have sugar in them just because they now they you know I'm not going to be able to do that. Now they you know is originally I was make I was trying to be disciplined and trying to change my diet but now they just don't taste good to me 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 I the way I even though I don't have a mechanistic explanation I just 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 certain meats for me I blame my Argentine lineage. I 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 that we're just bouncing around the carnival that is the microbiome and nutrition because I think that these 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 go back to the fiber but I want to make sure that we close the hatch on this issue of fasting and cleansing 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 the current microbiota out of their first is that correct yeah you know 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 like this you know the studies haven't been done and to me wiping out this microbial community unless it's done with like 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 you know playing the lottery a little bit and so so I think you know I don't want to say that those 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 you know out there it 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 can't say that it's something great to do I I can't imagine a future where as the microbiome gets incorporated into this you know emerging paradigm of precision health you go into a clinic somebody types your microbiome and says oh there's a this huge massive misconfiguration you have all these ingrafted bacteria that live that are residents and you got 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 no or compatible with your human genome and can be reinforced with a diet that we know is good for you will install those microbes will help you along in the diet to note so you know how to nourish those microbes and that will be the way that you can figure your got microbiome so you know I can't imagine a future where that sort of flushing 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 end of last year about comparing the inflammatory so inflammatory markers of people who ate a certain amount of fiber or certain amount of these fermented foods this study is amazing for several reasons but almost as amazing is 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 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 emerge 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 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 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 and even though I'm not certainly not expert in microbiome give you the opportunity to share with me and me to ask the kinds of questions that have zero agenda I do like sourcrout 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 food industry yeah absolutely yeah yeah great yeah wonderful and an important note there is is the one you pointed out that this is an incredible collaboration with Christopher Gardner's lab and you know a bunch of people Erica Saunemberg helped lead this study and then 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 take 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 a piphany that we we had while studying the got 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 emeliorate 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 you know that's the way medicine is practiced and that's become less successful over time as we moved into this era of inflammatory Western diseases and you know with the exception of the current pandemic that's you know sweeping the world you know 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 hard diseases and inflammatory disease you know the list goes on and on and and so we started to think a lot about like how can we get out in front of this how can we think about like preventive 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 the at the basis of a lot of these diseases 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 develop an inflammatory disease leading to better longevity and health over the course of our life so we were you know studying this in actually in mouse models and realizing that you know 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 launch to the 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 to find what a healthy microbiome is and monitor the immune system in great detail and so there are 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 house themselves you don't have to pay that's true that's true yeah those that can afford housing of course yeah for yeah sadly just for that portion of the population the so Christopher's group were they were our masters are 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 hold maker 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 are 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 you know hundreds to thousands different 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 six goes up or down but to be able to see all these facets of the immune system changing 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 and immune system and if we put them on a high fermented food diet a diet rich in live microbes and all the metabolites that are present from fermentation and foods how would that change microbiome and immune system could you give us some examples of what those diets look like and were you changing their basal diet or you just adding things on top of what they were already eating so it's hard to change people's diet it's very hard to trust that they actually do it and they're not sneaking and totally yeah and so we and you know we've started the 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 and probiotics microbes delivered in pill form prebiotics which are purified forms of fiber and in those cases we actually can have placebo groups because you know it's 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 because 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 you know from 15 to 20 grams per day up to over 40 grams per day so can you kind of 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 you know I will say that getting back to the you know Christopher's rule for a healthy diet a lot of the macron 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 a lot of changes that are known to be beneficial kind of 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 you know foods that you could buy at a grocery store that were naturally fermented and contain live microbes and so this you know largely consisted of yogurt a keeper a sourcrout kimchi you know some fermented vegetables kind of brain fermented vegetables pickles pickles things like that but but they do you know one of the things that I think is a pitfall in choosing fermented foods is you know 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 our cucumbers that they've put in a cedar acid and vinegar to reconstitute that fermented flavor but there's no live microbes involved in that and even sourcrouts 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 and so if you want to 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 refrigerator section essentially and I'm really glad you pointed this out because you can find sourcrout on the non fermented non refrigerated shelf that is indeed non fermented a lot of fermented foods that are available in the US can be high in sugar so was there any instruction as to you know getting people to make sure that they were consuming yoghurt that weren't loaded with sugar or did you let them just select for the stuff in the cold the cold section that is fermented no it's super important point we we instructed people to eat non sweetened yoghurt the you know it's I think a huge pitfall in this area as 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 of 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 you know plain yogurt which they didn't like just kind of neat we would mix in like a little maple syrup or honey just a little bit and gradually we reduce that over time to the point where their palate adjusted now they just really like plain yogurt but it is you know 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 here 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 call it and kombucha can have small amounts of alcohol in it but you know we yeah kombucha actually was one of the major things that people drink during the or consume during the fermented food phase and the you know that the deal with with beer is that there may be beneficial properties of the microbial communities and naturally fermented beer but most the beer that we buy again is canned and filtered and there's no live microbes there so very different than if you you know siphoned it off of your home brew and drink it probably that if you buy it in the store I just 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 I'll just refer people to a resource in Tim Ferriss's book The Four Hour Chef he actually gives an excellent recipe for making your own sourcrout which basically involves cabbage and water and salt but you have to do it properly because you can grow some not necessarily lethal but 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 as we get them which is a ceramic that you can see can make large amounts of truly fermented sourcrout 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 to anyway just to refer people to a source that's very low cost compared to buying the high quality fermented foods even kombucha is something you know it's like $5 a bottle of you know this much and if you consume liquids the way I consume them that's kind of a that's just the big the start so yeah and but you know if you can get your hands on a scoby kombucha is another one that's super simple it's like you can grow your own you can 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 and it's just you know it's a it's a scobies a symbiotic community of bacteria in yeast that you you know you you brew tea you add sugar to it and you put the scobion and you wait a week or two depending upon the temperature and you then you just you know move the scoby over to a new batch and you're old what the scoby was in is kombucha and it's it's wonderful I love it I would love it if members is already in swed start to make their own kombucha and sauerkra I I've been having so much fun I don't do it but you know it's done in our home I don't I don't go anywhere near the food production and as it's for everyone's benefit so how much fermented food and then were they consuming and because you mentioned the number of grams approximately of fiber and but was it even servings ounces how many times a day early day late day right yeah so the we had a wonderful dietitian instructing people for this and her name is Delia Perlman and she really was the key and is the key for many of our studies for getting people to eat differently and you know I the general instructions were for people to eat as much fermented foods as possible more as 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 we you know the dose was excessive and not easily achievable by a lot of people in the end we can go back and say okay this is this is the point at which we lose the biological signal but people during the height of the intervention phase the six weeks during the height of that were up over six servings on average per day of fermented food so kind of two servings at each meal and the you know ounces or weight or size it really dependent 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 they were buying you know for a kombucha be like a six to eight ounce glass sourcrout like a half cup or something like that and same with yogurt. Right so what what were the results? Yeah so the results astounded us in a way but then thinking more deeply and it will be evident even after I explained 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 we all the mouse studies have told us that high fiber really leads to a much healthier microbiota can lead to positive changes in the immune system and in fact even when we had a little bit you know we had wonderful donor support but still 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 like live microbes should be exciting and 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 different methods 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 and western human we saw this increase in the 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 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 health 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 got microbiota diversity through the fermented foods and the this massive immune profiling and we see you know a couple dozen immune markers inflammatory markers decrease over the course of the study so we multiple we measure these at multiple time points throughout the course of the study and there's kind of this step step wise reduction in things like interluchin six and so interluchin twelve a variety of kind 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 an attenuation of inflammation so that's 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 so the complete protocol I think was fourteen to seventeen weeks or something like that the actual intervention phase consisted of a four week ramp and then a six week maintenance period and then the second question itself was ten weeks but there were six weeks of really kind of hardcore high levels of fiber or fermented foods yeah and I glad you mentioned the ramp because my experience with fermented foods is that you can be beneficial to give the system an opportunity to acclimate I mean if you consume a giant bowl of sourcrout it's not going to be the worst day and night of your life but you'll you'll know you did totally just leave it at that and so you want to kind of acclimate to it and then at that point now where people 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 that the sourcrout has been stewing in and I get I like to think that I consume some fermentation that way it's salty it acts as kind of a post training replenishment but if I had done that six months ago straight off I think it would have been pretty rough on my system I started taking little bits of it and then adding it each day totally and so both the fermented foods in the fiber it's well known that this kind of gradual ramping is a really important way of mitigating bloating and other kind of digestive discomfort that can happen when you're 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 you know we did this in a very delicate way to get people up to the high dose the brine question just a tangent here and I think that I'm going to do that. A tangent here for a second that was actually one of the products that we had people used in the fermented food phase there's actually a product called gut shots which is just the brine from 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 got microbes or the fermented fermentation microbes and the nutrition microbes removed or present into mice and looking at changes in their mucosal immune system so we're studying this in detail now because this is 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 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 the things that I'm going to do is I'm going to do that. I'm going to do that if you really think about some of them are exceedingly expensive but the what what I described before with making your own. Combucha is it's not quite brining but the homemade sourcrout that protocol is out there as I mentioned in Tim's book the the four hour chef and you get a lot of the brining from from that an almost endless amount of the questionary 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 you do not recommend doing that some of these it's very potent it seems and you can consume you know even a half an ounce or an ounce. Yeah very I mean very potent from the standpoint of fermentation but also very salty so you know there's a lot of effects that can yeah don't do what I do at least not at the outset and but 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 who were initially in one group or the other move to a different group. Well so we for you stop and then return yeah we we actually just did a stop and followed them during a washout phase and I 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 or was 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 to it put her feed you'll be able to find him reporting some of the the early results of this study. Give us a snippet of was there a superior just give us a you know how to tell us which one but was there a superior condition of either Mediterranean versus ketogenic. So I should 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 he's his group is put together from this is largely independent of the microbiota data and now we're doing a more in depth analysis and I'll have more to say about that the future but that return to that 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 day. So we had complete control over what they at least had available to eat and then the second phase they they make the food on their own and then we cross over and do the same thing and so that's really like the 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 wash out phase where people we didn't make them stop eating and we didn't have a lot of time to eat. 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 and many of these people so there does appear to be like 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 the best one of the investigators involved in the study that all it's great to go direct to the source. Annacdotally where their improvements 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 Access 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 actually basically how signals get out of the gut totally so did people I certainly notice that when I'm eating more fermented foods or there's probiotics in some in drinks I consume and so forth that I feel quote unquote air quotes completely subject I feel better. I wish there was an objective measure of feeling better but I seem to think more clearly sleep better mood etc and I know I'm not alone in that and people and anytime 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 do people say they were feeling better in any way and if so what did you observe and again we're highlighting these as Annac data. As part of this effort to look at how dietary interventions affect our health and well-being and so forth in microbiome and immune system we interact with a lot of people who have like read our book or you know 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 you know tons of people say they have more energy they think more clearly they sleep better they're not. So sleep better their family is nicer to each other like the number of crazy things and it's really hard done couple like is this because you know these people have taken charge now what they're eating and just feel better in general for being in control of kind of what they're doing or is there this cascading set of effects that are actually you know impacting our you know kind of emanating from the gut brain access and so we actually implemented a bunch of questionnaires and even a cognitive test to try to. Get it some of this and I should say you know that the list of this goes on and on their people who claim that their complexion improves and that their you know allergies and there's probably all sorts of ripple effects if you can affect your inflammation you can we know that you can affect your cognition we know that you can affect your you know your your skin and inflammation that's occurring on your skin so 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 it's not going to be a good thing to do. So we're going to do a study and in a small you know 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 you know all of the things that that we were testing for which yeah there could be a variety of explanations for that the you know we also have a standardized stool measure that people use and there was you know kind of 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 psychoanalysts would have a field day with that. What sorts of interesting things did you observe in the fiber group because it's clear that that group yielded some unexpected findings in both directions that things you expected to see you didn't see as 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 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 kind 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 of the really interesting part is the people with the highest diversity got microbiomes to start the study were the ones that were most likely to have the decreases in inflammation and so the you know data seem to be telling us that if you start off with a diverse microbiota maybe one that's better equipped to to degrade a wide variety of dietary fiber you're more likely to respond positively to it if you have a very depleted got 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 you're not able to respond to it that even if we consume a high fiber diet at least for a short period of time we don't have the right microbes and are got 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 you know within nine months but certainly over the course of years immigrants that come here lose a lot of the diversity in their got microbiome but a lot of the fiber degrading capacity in their got microbiome too so it could be that over time this becomes a one way street and it's hard for us to recover the microbes that that actually can degrade the fiber 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 you know have lost these microbes in their in some ways irrecoverable without deliberate reintroduction of fiber degrading microbes I recall from childhood there were kids that would eat dirt and snails and so that just sounds totally disgusting but you know kids covered with mud and you know that maybe not so much anymore and certainly during the pandemic there's been a lot more use of these hands sanitizers that prior to that people seem pretty spooked about but then obviously they prioritize them so it did you well you have children did you do you encourage them to to when they were young did you encourage them to interact with pets and dirt and stuff in the environment provided that stuff wasn't immediately toxic exactly so this is really you know it's it's a continual cost benefit analysis I think the I will say that you know with the pandemic now and certainly just with infectious diseases and general it's really important to be aware of you know the the possibility for compromising your health through the spread of germs and so that that is just you know hand washing is important and we have to be careful with you know the spread of germs but I do think that you know the the sanitation sanitization of our environment has gone overboard with the you know various things being impregnated with antibiotics you know shopping carts and things like that and toothbrushes and you know it's it's like antibiotics and and you know things for killing microbes are everywhere and when we were raising you know when our daughters were young and we're we're making these decisions that we would make were really one how likely are they to encounter a disease causing micro if we've been out you know on a hike or in our garden you know 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 there's 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 you know certainly if you've been in the grocery store on the subway probably good idea to wash your hands but I so I think you really need to think about kind of the context of it and 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 that the fermented food result that we saw is a way of taping the food and we're going to do that. So we saw is a way of tapping into the same pathways kind of an environmental exposure to microbes that's safe interesting 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. So we're signaling and transport from the gut all along its length as far as I know into the blood stream into other organs and tissues so for the immune system. It seems straightforward. Could reduce the amount or number of inflammatory cytokines like aisle six and so forth maybe increase the anti inflammatory cytokines like aisle 10 and others but we know there's a got brain access and neurons that literally talking both directions between brain and gut but let's say I eating my fermented foods I'm doing all the right thing. And I'm doing all the right things and I'm my gut is diverse and I have all the good goodies at all the right places. How is it that the 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 get feel better or I might get sick less often or combat any illness more quickly. How is that actually happening I mean is it is it that the microbiota stay restricted to the gut but the signaling molecules are all downstream in a downstream way or are making good or bad things happen. Whereas there's some sort of direct recognition at the body level or there sells in the body that are responding to 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 is kind of metabolic inputs what we're eating and what other microbes are present in the environment providing molecules to them. So you know it's this complex matrix but we you know that probably the simplest place to start is just the immune system we have an immune system that you know 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 you know they're 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 be can be. Can become opportunistic pathogens and so the immune system really playing an important role to keep you them in place is essential for the system not moving into a disease space the immune system has a variety of ways of of monitoring what microbes are there they're actually specialized structures in the gut known as pyres patches that actually take up microbes they they actually allow microbes to transit into this. So the immune system really plays a role in the immune system and we're going to do 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 so kind of like a border patrol exactly yeah so they they bring them in they they you know fingerprint them and then you know have have kind of this you know set of responses ready to go if needed amazing there are other cells known as dindritic cells and then they're going to be able to do that. Other cells known as dindritic cells special types that actually send long arms these processes out into the lumina 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 specialised proteins that perceive patterns that the molecular patterns that the microbes make so things like endotoxin lipo polysaccharide just the cell wall of the bacteria we have specialised 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 kind 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 you mentioned before this direct response. So there are these direct you know these cell types that express taste receptors in the gut and have ways of sampling dietary components there 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 you know in addition to that there's this tremendous tremendously important in taric 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 what actually is is happening do I need to interact with immune cells so there's this really complex array of 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 you know get into the blood cycle through and and then home to other regions of the mucosal surfaces so that mucosal surfaces are educated broadly against what's what's passing through our gut so there's 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 blood stream directly and so you know the the array of molotovs and the array of molecules is still being defined we're trying to figure out what all these chemicals are we mentioned the short chain fatty acids but those are just the tip of the iceberg they're really interesting compounds like you know end old derivatives and phenols and and you know derived from amino acids metabolized by got microbes taken up into the blood stream and then we further metabolize these they become kind of co micro host metabolites and then they can go on and bind to different receptors throughout our body anywhere blood stream has access to and start to trigger signaling cascades is it known whether 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 access 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 in autism spectrum disorders maybe even an 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 gut that the microbiota themselves are manufacturing chemicals that can make into the blood stream and therefore I'm asking if those chemicals can move from the blood stream into the brain directly it may not be a gut brain access via neurons it actually could just be seepage of serotonin into the brain or to see to calling into the brain for that matter totally yeah and you know the the the biology of most of these molecules is not well understood but certainly in like cerebral spinal fluid that's been analyzed it's you can perceive these microbial metabolites so they are there that's the answer yeah some some of them are getting across the mirror but so 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 the way into the blood stream eventually are excreted through the kidneys and 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 those many of those originated in your gut from your gut microbes but people with kidney disease whose kidneys filtering processes not functioning properly actually build up high levels of many of these metabolites into the blood stream 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 found at the blood brain barrier for shuttling the molecules back into the blood stream if they do get across and we know that like mental fog is a big 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 the central nervous system amazing I'm glad you mentioned mental fog a few years back there were some reports some scientific reports and as a consequence in the media that excessive intake of probe 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 as a consequence of the work that you and Chris published but 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 yes I'm 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 you know probiotics and one of the more expensive supplements out there you can quickly get into several hundreds of dollars per month if you're getting the quote unquote best quality ones right and if they're going 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 I mean there's just people know that they I think the many of these companies are aware that they 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 that they, what is in there does not match what's on the label. So then 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. 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 it's, 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 can't, 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 micocell 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 meta-analysis that do suggest in certain instances recovery from antibiotics that there are even though it may cause your microbiota to recover more slowly that it may actually prevent a diureal disease, recovery from viral diureus, 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. 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. So if you're experiencing a medical problem or want to consult a doctor, 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 for as a place to start in this space, I think. And what about prebiotics? Is there a number of reasons why I can imagine that prebiotics would be beneficial? Which essentially you're pushing the fiber system, which we talked a lot about today. Yeah, absolutely. You know, 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 microbiota diversity 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 or 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 is 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 a type of thing where you have to try to find the thing that's right for you. But there are also our studies that suggest that if you layer rapidly for menable 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 hepatocelular carcinoma when they're fed a high dose prebiotic liver cancer 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, they're 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 is it fair to come back to this idea, trying to 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 and also fire. Sounds like some fiber is good and despite the outcome of the study, you identified that if you have the appropriate microbiota, then you will background, then one will respond even better to the fiber, maybe a longer ramp up phase for those folks and then the fermented foods because 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. So 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 because I sort of know where you're trying to what, well, is it blood draws that you used to measure the inflammatory? Exactly. So we do blood draws like the two stone. Yeah. 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 you and your wife who co-run your lab. You have a book on this topic. Could you tell us about the book where we can learn more about the San Enberg 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 where I was looking for, you know, willing participants. Yeah. So Eric and my wife and I wrote a book called The Good Gut and that really was a response to how we were changing our lives and response to being in the field, being very familiar with the research. I think that a lot of our friends that weren't studying, they 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 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 just, 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 kind of the science in the field and just lay a foundation for people if they want to start thinking about these changes. And then in terms of kind 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 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, but 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 those are people that work on infectious disease and like all the bad stuff. So it's interesting and really important that people realize that we're carrying all this vital cargo and we need to take care of the cargo so we can take care of us. So thank you so much for your time and for the work you do and I hope we can do it again. Thanks Andrew. This was the great conversation. Terrific. Thank you for joining me today for my discussion with Dr. Justin Sonnenberg all about the gut microbiome and how to optimize your gut microbiome for health. Please check out the Sonnenberg Lab webpage. That's Sonnenberg spelled S-O-N-N-E-N-B-U-R-G-L-A-B dot Stanford dot E-D-U. That's Sonnenberg Lab dot Stanford dot E-D-U. They often recruit for studies exploring how different aspects of nutrition impact the gut microbiome. Much as we discussed during today's episode, please also check out the book that he and his wife Dr. Erica Sonnenberg 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 anyone 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. Guess 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 slash Andrew Huberman 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, got 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 Thor and that's Thorne THORN 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 THORN or any dot com slash the letter U slash 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 dot com slash U slash 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. 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