Welcome to episode 11 of Eat Your Greens with Dr. Black, where you learn just how big a nerd Dr. Black truly is. This episode is all about your microbiome. That's the microorganisms that live on and in your body: especially your gut. If you watched the recent Netflix documentary, You Are What You Eat, where they studied twins, you may already know some of this. I had so much fun researching this episode. I have a bachelor's degree in microbiology, and I still find the complex world of microorganisms to be so utterly fascinating. Virtually none of what I cover in this episode had been discovered when I was in medical school. I'd like to give a quick shout out to my office, mate Dr. Jurak for putting up with me while I researched this episode. She was trying to diligently work on her charts during lunch, and I kept interrupting her to gush about some super interesting thing that I learned like - get this - shotgun metagenomics.

I mean, that's just fun to say: shotgun metagenomics! So, thanks to Dr. Jurak for putting up with me. I know between making her listen to K-pop and interrupting her with fun facts about the microbiome, she is probably about ready to find a new office mate. But I appreciate her patience.

So, we knew that the colon is full of bacteria back when I was in medical school. We mostly thought of those bacteria in terms of diseases like dysentery or cholera. It wouldn't be until over 20 years after I graduated that the technology to identify many of these microbes in our large intestine would be developed. And that means we had no ability to understand the impact that the microbiome has on our health. Both in terms of causing and preventing disease. Nowadays, the microbiome is a hot subject for research. A Google search for articles on gut microbiome just since 2019 yielded me 168,000 results. And while I was in the process of writing and recording this episode, new findings were being published almost every week.

We now know that the microbes that live in your gut not only affect your digestive health, but also influence your immune system. They regulate your blood sugar, they can alter your sense of taste and impact your food cravings, and they can modulate your risk for cancer. They may even play a role in how you age.

So, what can you expect in this episode? We're going to start by learning what the microbiome is and some amazing facts about your GI tract. I'm going to cover a little bit about the history of how the microbiome was discovered. (Spoiler alert, pediatricians paved the way!) And then without getting too technical, I'll explain how scientists study it. (That's the shotgun metagenomics part.) Last, I talk about how the bacteria in our intestines affect our health.

To help me explain all of this, I sat down with Dr. Micaela Vargas from the department of biology at Texas state university. She and I had a super fun conversation about gut bacteria in babies, in hunter gatherer tribes, and we also talked about some simple things that you can start doing today to keep your microbiome happy and healthy.

Before we get into my conversation with Dr. Vargas, I'm going to give you a quick introduction to your GI tract and a bit of the microbiome backstory. So, get ready to learn some crazy interesting facts about the microscopic drama playing out in your very own body.

As a reminder, this podcast provides general health information about nutrition and feeding of infants and children and is meant for educational purposes only. It is not intended to replace the important relationship between a parent, child, and pediatrician. If you have concerns about your child's nutrition, health, or growth, please consult your doctor.

If you've listened to any of my episodes, you know that I often like to start with a definition. So, let's talk about what we mean when we talk about the microbiome. Basically, on your body, there are many types of organisms, even in parts of your body that we once thought were sterile.

Every region of your body has its own ecosystem of microscopic organisms, and these include things like bacteria, but also viruses, fungi, amoeba, and these primitive organisms called archaea - and even a variety of tiny mites that live in places like along your eyelashes.

Humans evolved alongside these tiny creatures and, for the most part a symbiotic - or mutually beneficial - relationship exists. We help them and they help us.

Sometimes the relationship is commensal. Commensal is where one organism is helped, but the other one is pretty much unaffected. Organisms in our microbiome have traditionally been considered commensals, but that might just have been because we didn't yet understand how they actually contribute to our health.

And then, of course, there are times where the relationship is pathogenic: where one organism benefits but causes harm to the other. These are the disease-causing bugs like the flu virus, salmonella bacteria, and athlete's foot fungus.

Let's review a little bit of the anatomy. What is the GI tract? Basically, the gastrointestinal - or GI - tract is a hollow tube that starts at the mouth and ends… at the other end.

Humans are basically one big, complicated pool noodle. The lumen is the inside of the pool noodle - or intestine in this case, and the epithelium is the single layer of cells that separates the inside of the bowel from the rest of your body.

The types of bacteria living in our GI tract vary from region to region. They change as you move from the mouth down to the stomach into the small intestine, and the large intestine. But even in different parts of the same region, you're going to see a different composition of bacteria. For instance, in the mouth, there's different types of bacteria living on the tongue versus the teeth and gums, versus what's floating around in your saliva, or in the back of your throat.

So, as I said, the gastrointestinal tract is a big hollow tube that starts at the mouth. When you swallow saliva or food, it goes into the esophagus. That's the tube connecting the mouth to the stomach. So then from the stomach, things move into the small intestine.

The small intestine is where most of digestion takes place. So, any material that's not digested in the small bowel is passed on to the large bowel, which is also called the colon. And by the time partially digested foodstuff reaches the end of the small intestine, about 80 percent of the water content has been absorbed.

The colon absorbs most of the remaining water, and it is also where undigested foodstuff is. Fiber from plant foods is fermented by the trillions of bacteria that make up our gut microbiome.

So, we have mouth, esophagus, stomach, small intestine, large intestine, and then finally at the end of the GI tract is the rectum. By now our food has been turned into poop, which enters the rectum signaling that it's time to go visit the bathroom.

All right, how about a few fun facts about the GI tract and the human microbiome?

Starting at the stomach: your empty stomach has the volume of less than 4 tablespoons of liquid. That's roughly 2 ounces. But it can stretch to hold a whopping 2 cups of liquid. The stomach lining is regenerated completely every four to five days. And that's because stomach acid, which is also known as gastric

acid, is super strong. It's predominantly composed of hydrochloric acid, and it has a pH of 1. 5 to 2. That's somewhere in the vicinity of battery acid. The small intestine is 22 to 23 feet long, whereas the large intestine is only about 5 feet long.

In your body, as an adult, you have about 30 trillion cells, whereas there are about 39 trillion bacteria living in or on your body. So that makes us only about 43 percent human. If we look at our own human genome - our DNA - we have approximately 23, 000 genes. But the gut microbiome collectively encodes over 3 million genes. And then if you look from human to human, we each have our own distinct microbiome that is as unique as your fingerprint. In fact, when they studied twins, twins share only 30 percent of the same gut bugs. Even twins that live together. We're not talking about twins separated at birth.

Last the colon is home to at least 1,200 different species of bacteria. And I say at least, because as technology advances, our ability to identify new types improves.

In fact, when I was researching and I did my Google search, I came up with many results stating that there are only 300 to 500 different species. And this is because up until very recently, we just didn't have the ability to identify them. Now we know that the tongue alone has over 700 different types of bacteria and is the second most diverse microbiome in the human body after the intestines.

Can you see why I'm just nerding out about this stuff? It's so interesting.

So. Why are the Google search results so out of date? What's changed? Let's go back to the beginning. It was first recognized that there are bacteria in our poop in the 1600s by Antony van Leeuwenhoek, the father of microbiology himself. But the significance of these bacteria, or animalcules as he called them, was unknown for centuries.

Once the germ theory of disease was accepted, fecal bacteria were mostly thought to cause infections or at best be harmless commensals. In the mid 1800s, our understanding of the importance of gut bacteria was advanced by the work of two pediatricians - Shout out to pediatricians! My peeps! - German born, Theodore Esherich and French Henri Tissier.

At only 29 years of age, Esherich published a book in which he described the bacterial composition of the infant GI tract, how it developed over time and the role of these bacteria in digestion. Tissier, on the other hand, used anaerobic

cultures: that's a way to grow bacteria without exposing them to oxygen, and this is important because most of the bacteria in our gut are anaerobic species - they grow best without oxygen. So, he used anaerobic cultures to study the gut bacteria, and he discovered that if you take bacteria grown in culture from the stools of healthy infants, and give it to infants with diarrhea, the sick babies were effectively cured. This is possibly the first known use of probiotics.

A hundred years later, a U. S. doctor reported the successful treatment of four patients with severe life altering C. diff infection. C. diff is something that lives in our gut, but it's kept in check by the other bacteria. So, in 1958, a U. S. doctor was able to successfully treat four patients with a severe C. diff infection by administering stool from healthy donors by way of an enema. That's called a fecal transplant. Yes, it's a thing.

So, unfortunately, despite these success stories, there really wasn't much progress in understanding the role that gut bacteria play in human health for quite a while. This is because it's really difficult to grow many of the types of bacteria that live in our colon outside of the human body. And you can't study something if you don't even know it exists.

So it wasn't until the technology that allows us to study the genome, the genetic material like DNA and RNA, was developed that we began to be able to unlock the secrets of the rich microverse existing within us.

In the 1990s, scientists from all over the world worked together to map out all of the 23,000 genes encoded by human DNA. But now think about the bacteria in your gut.

Up until recently, it was thought that there were 300 to 500 species of bacteria living in the human gut, because this was what we were able to grow in culture in the lab from stool samples.

The average bacterium has between 1,500 and 7,500 genes. So, if you do the math, that's anywhere from 450,000 to as many as 3.75 million. That's genes just in 300 to 500 species of bacteria. So how the heck are scientists supposed to study all of that when it took over a decade and the concerted effort of a global team of scientists to decode the measly 23,000 genes of the human genome?

Of course, what we needed was even better science. Fortunately, a technique called next generation sequencing was developed, which has given us the ability to survey the genomes of entire microbial communities and compare them to the genomes of known organisms.

Shotgun metagenomic sequencing: (hooray, my new favorite word!) shotgun metagenomics uses next generation sequencing to sequence all the genes in all the microorganisms present in a sample without the need to cultivate individual species in the lab and study them one by one. And this allows scientists to identify and classify bacteria.

It's thanks to this new technology that we now know that there are well over a thousand different species of bacteria making up the microbiome, rather than that 300 to 500 that kept coming up in my Google search.

Are you still with me? We've learned about the GI tract and what a microbiome is, and we've caught up on the science that helps us study it. Are you as excited as I am about all of this? Do you also want to grow up to be the kind of scientist that does shotgun metagenomics? Dang, I think I missed my calling!

Now that we know more about the fascinating backstory of the gut microbiome, let's hear what a molecular biologist has to say and learn more about what these tiny creatures can do for our health.

Dr. Black: I am really excited to welcome Dr. Micaela Vargas today. Dr. Vargas is currently on faculty at Texas State University in the Department of Biology, where she teaches some really fascinating courses. Her subjects include the human microbiome and also the molecular biology of aging.

Dr. Vargas was the first in her family to graduate from college, and from there she went on to get a PhD in cellular and molecular biology from the University of Texas, San Antonio. Her research has focused on cancer, infectious disease, and regenerative medicine. She's founded a genomics consulting group, and she's a self-described STEM-preneur. I really love that phrase, STEM-preneur. That's awesome.

So, in addition to all of her teaching responsibilities, research professional duties, she's also the National Co-Chair of Young Women and Bio, and she's an advisor

for several student organizations, including Latinas in Research and the Minority Association for Pre-Health Professionals.

Thank you so much for joining me today, Dr. Vargas. It is really a pleasure to have you on the show.

Dr. Vargas: Thank you, Dr. Black. Very, very thankful for this opportunity. And just to kind of thank you for that introduction by the way. This is wonderful. And just kind of prepping for this, we were going back and forth and have a lot to talk about today, but I kind of want to get into, um, the gut microbiota and just to kind of segue into the science of it, but just to kind of let your listeners understand why your gut and the microbes in your gut are very important.

For one, they promote digestion by facilitating the absorption of nutrients. And sometimes we cannot get these nutrients, alone. So, we need the aid of the microbes in our gut to, to facilitate that. And then two microbes are very, very important for the digestive tract because we need our GI tract to function properly.

And without these microbes we basically have diseases because of that disruption. And then three, uh, these microbes create a very important barrier against pathogens and toxins. And pathogens are just microbes that are out to cause harm. And they're not necessarily there to have this symbiotic relationship. And so, we need the addition of these important microbes to protect us against those toxins. And lastly, the microbes play a very, very important role in defending you and basically, developing an important relationship with your immune system. And that immune system - or basically the microbes - are your protection and they signal the immune system if there's any pathogens or players involved that are out to cause harm.

And so just with those four different functions, and there's numerous others, but these are the main four. Um, it's no wonder that scientists have now paid very close attention in the past 20 years that our gut microbiome is a normal breathing additional organ that we have to take care of.

Like how does one develop and maintain a healthy microbiome so that the four that I just discussed before is maintained throughout our longevity. And so, I taught, a microbiome class a couple years ago and one of my favorite subjects. And in teaching my students you inherit your microbiome from your mom. And that makes a whole lot of sense because as a fetus, you are developing in this

environment. And throughout your mother's gestation it's very important (especially, you know, going through pregnancy) the diet, being exposed to antibiotics, host genetics. What are those genetics that are contributing to that microbiome? What is the host being infected by? Um, and then the different maternal stresses and the environment that this mother is experiencing. And then throughout development and then during delivery, depending on the mode of delivery is going to be very different in what microbes you're exposed to.

Dr. Black: I agree it's so fascinating how it develops and all those stages that you discussed. What I learned in researching for this episode was that the infants' microbiome starts developing even in the womb. You know, we used to believe for centuries that the placenta and the womb inside the amniotic sac was sterile.

And what they've discovered is the microbes in the mom's gut start changing during pregnancy, and they've seen an increase in the different organisms that the baby will need. So even during pregnancy, mom's gut is starting to be populated with these organisms that the baby will need to digest human breast milk.

And it's thought that some of those organisms can leave the mom's intestine and actually cross the placenta and get into the amniotic fluid. And then there's those postbiotics, right? The things that our gut bacteria make - the short chain fatty acids - and they also, of course, enter mom's bloodstream, cross the placenta, and start having effects on how the baby develops.

So, it's, it's really fascinating. Even before birth, we're starting to develop a microbiome. And then, as you said, all of the things that affect the mother, her social determinants of health, her environment, her diet also play a role. And then we get to the actual, the time of birth and when the baby's being born and whether or not we're having a c-section or a vaginal delivery.

So that's an important time. If you want to tell me a little bit more about what happens during the birth process.

Dr. Vargas: So, the mode of delivery is going to determine what exposure of microbes that this child is going to experience. And like you mentioned before, mother has their own microbiome. And the thought process is that yes, this child is inheriting their microbiome from their mother. But when baby, through natural birth, becomes colonized by the mother's vaginal biota. So just having that contact and the rupturing of the maternal membranes is all exposing that child to the

natural flora of the mother. However, let's say babies are born via cesarean section and well, they're not being exposed by the vaginal biota. Well, how they're exposed is the adult skin. And this is why they say skin to skin contact with that newborn is very important. There was earlier studies that were done with c-section babies. And they would take swabs, swab the mother's vaginal biota, and then would swab the child mouth, ears face, no, pretty much everywhere as if it were mimicking going through the vaginal canal or birthing canal. It showed that those exposures of the early vaginal biota that did improve these children's, um, own microbiome.

And then through infancy again, between zero and three years, the child is still, you know, developing their microbiota and, that's pretty much the window of opportunity for microbe, modulation being exposed to pretty much everything.

So, whether it's the maternal diet, if the mother is breastfeeding what is the family lifestyle? What is the geographical location? And then you mentioned earlier Dr. Black with the social determinants because a lot of that has to deal with the contribution of the child's microbiome and it's only stable during adulthood. And then as we age, those, um, microbes tend to disperse, but we'll talk a little bit more about thatlater.

Dr. Black: We'll get back to that.

Speaking of the environment that the child is raised in and those social determinants of health, when they've looked at the microbiome of infants in urban settings, developed countries - what we're seeing is actually a loss of one of the really important types of bacteria, *Bifidobacterium infantis*.

This bifidobacterium is really important in the infant's ability to digest human breast milk, the human milk oligosaccharides, and we are losing that bacteria in the guts of infants in developed countries compared to in less developed countries. And it's being replaced with a different strain, a different species of bifidobacterium, *Bifidobacterium breve*.

And this species is less efficient at digesting human breast milk. And I know I have seen a huge rise in digestive issues in infants: in milk protein allergies, in failure to thrive where infants aren't gaining weight and thriving on breast milk.

And the mom is having to stop breastfeeding and switch to formula because the baby's just not doing well, just not thriving. And it's been a really interesting

phenomenon. When I started practicing pediatrics, I'd never even heard of some of these specialty formulas that we use now. And a couple times a month I'm switching babies to these formulas because they're just not tolerating the intact milk proteins.

So, it's been a really interesting phenomenon over the last 20 years and there's definitely been a huge difference in the gut microbiomes of infants delivered vaginally versus by c-section. Although I came across an interesting finding that questioned some of that. When they looked at rates of some of the neurologic diseases in c-section babies, there did seem to be an increase in autism, ADHD, disorders like that in children who had been delivered by C-section. But an interesting study was done where they compared infants delivered during an emergency c-section where the mother had general anesthesia to a c-section where the mother had a local anesthesia, and they did not see the same findings.

So, it's definitely more complex than just the microbiome. You know, what kind of anesthesia was given, the stress that the mother was under during the time of delivery that led to the emergency C-section: all of that is also going to play a role. But it's clear that the microbiome of the two sets of infants- c-section or vaginally delivered - is markedly different.

I definitely think the impact on the immune system - ou were talking about how the microbiome interacts with our immune system and how important it is - and we see higher rates of allergic disease, eczema, asthma, and seasonal allergies, food allergies in c-section, babies to be sure.

Dr. Vargas: Yeah, I mean it's, it's all fascinating. And, you know, going back to the bottle feeding versus the breastfeeding infants one of the early studies, and what they did was they studied the gut microbiome from the last hunter gatherers from Africa called the Hadza Tribe. In this hunter gatherer study, they did a study between people from the United States who are on western diets.

And then they compared that with the Amazonas of Venezuela and then of course the Hadza tribe. And what they found was between the Hadza Tribe and the United States is that we have around 1200 species of bacteria. When you compare that to the Hadza Tribe, and the Amazona's is well above that: close to 2000. So, they clearly have a lot more of the gut bacteria that we need. And then when you count the grams of fiber per day, we only get about 15 grams if that per day, um, compared to the Hadza Tribe - anywhere between 100 and 150.

Dr. Black: It's a really interesting point and I, I kind of alluded to that in one of my earlier episodes about fad diets - one of the diets I mentioned was the paleo diet, right? Which is supposedly based on these ancient diets, but they cut out, one of the main things they cut out of the paleo diet is the grains and the starchy vegetables which are really important sources of fiber.

And they are big sources of the diets of the few still existing hunter gatherer tribes that we've been able to study. And it really highlights the importance of those foods in our ancestral diet and how cutting those things out has really had a negative impact our health - in particular as it pertains to the microbiome - because, as you said, we are losing bacterial species, and the diversity of the bacterial species is so important to our health.

Dr. Vargas: You said the word diversity. Gut diversity is so important and that's what the study found. And within that study, they also compared what bacteria were present and obviously the high bifidobacteria as well as other, but when they really honed in on the Hadza tribe, they found a bacteria called treponema. Treponema is very, very important. It's important to protect the gut. And we don't have this, and it's alarming. And so, in addition to that more than 33% of the microbiota in the Hadza tribe remain undefined, or unidentified.

Dr. Black: So, while we're on the topic of how the gut microbiome develops…

Once solid food is introduced at around six months of age. The microbiome shifts until age three to gradually align with that of mature adults. Although the types of bacteria in your gut change over your lifespan.

I tell my patients to pretend that they have a pet tortoise that lives inside their gut. In case you didn't already know the difference: Turtles are aquatic and they eat a variety of plants in addition to small fish and insects, whereas tortoises are land-based, and they eat a vegetarian diet and can live to be well over a hundred years old. It turns out your gut bacteria, like many of the same foods as tortoises.

So, I tell my patients that they need to feed this tortoise as if it were real Tortoises eat lots of vegetables, especially the green leafy kind. As well as a variety of fruit. So, if you take care of your tortoise, it will take care of you.

So how does this metaphorical tortoise- those trillions of bacteria living in your gut- affect your overall health? Let's start by grossly oversimplifying things. We now know that there are many types of bacteria in the gut.

Simply put. The fiber in our diet is called prebiotics. The prebiotic fiber feeds the bacteria that are the probiotics, the good bacteria, and then those probiotic bacteria go on to secrete post biotic molecules, mostly things called short chain fatty acids that communicate with and act on the cells of the human body to create a variety of effects.

When we eat the standard American diet, which is typically low in fiber high in animal products and high in ultra-processed foods, we support types of bacteria that also secrete molecules, but these substances are pro-inflammatory. They've been linked to cancer, auto-immune disease, heart disease, and diabetes. So, everyone has a mix of these good probiotic bacteria, and pro-inflammatory bacteria. When we establish healthy lifestyle habits, the proportion of the health promoting bacteria is greater than that of the disease promoting bacteria.

So, the good guys keep the bad guys in check. If we don't support a healthy gut microbiome, the bad guys take over, and this is called dysbiosis. The classic example of this is Clostridium difficile or C diff infection. So, when patients are treated with strong antibiotics, the numbers of the good bacteria decrease, allowing C diff to overgrow and cause a disease called pseudomembranous colitis, which gives you chronic debilitating diarrhea.

They can go on to develop dehydration, kidney failure, or something called toxic megacolon, and they may even die. This is the disease that we talked about earlier, where the doctor was able to cure it back in 1958 with the first known fecal transplant. The concept is simple. You deliver the microbes from a healthy donor directly to the colon of the sick patient, thereby re-establishing the ratio of healthy to unhealthy species of bacteria. Unfortunately, this treatment was largely ignored until the last couple of decades.

Fecal transplant is now an approved treatment for people with severe life-threatening C diff infection. And it has a very high cure rate after just two doses in most patients.

So, what happens when the probiotic bacteria make these postbiotic short chain fatty acids? You know, those molecules made when we give our tortoise plenty of

fresh plant foods. At this point, I think you should push the pause button on the episode and go make a bowl of popcorn, because we're getting into the really fascinating stuff.

When undigested fiber reaches the colon, the bacteria digest it for us, and they release the short chain fatty acids. The main ones are acetate, propionate, and butyrate. I get so excited when I read about these amazing compounds. These are the molecules now thought to be responsible for many of the amazing health benefits associated with eating a plant-based diet.

The growing body of evidence on the effects of short chain fatty acids is crazy. You will hear more about these incredible benefits your overall health in many more Eat Your Greens episodes to come. So, let's get back to my conversation with Dr. Vargas and learn more about dysbiosis, short chain fatty acids, and their effects on your risks of serious diseases like cancer.

Dr. Vargas: So, how do we maintain this gut health? You know, Dysbiosis or imbalance of the gut is, is basically not maintaining that diversity. So, we don't have the diverse microbes in our gut, we can start seeing a lot of these chronic inflammatory diseases like IBS, Crohn's disease, even cancers, and, you know, a whole slew of these aging diseases. And so, there was a, a study on, on mice.

These were called the Gnotobiotic mice. And what they did was they had these mice in a controlled and sterile environment, and they gave one mouse a fiber rich diet. And that mouse with the fiber rich diet had a very nice mucosal layer that protected the gut. It had a very diverse range of microbes. But then when you compare that to the mouse that was given a fiber free diet: massive dysbiosis, massive imbalance of those microbes. And the majority of those microbes were those that ate up the mucosal layer and started eating into the digestive tract. And so, this is how we get an, an influx of inflammatory diseases because of that.

Dr. Black: And just to go back, earlier in the episode I had talked about how we're, we're kind of one big complex pool noodle, right? The, the lumen of the intestine is the inside of the pool noodle, and that's where the all the microbes live. And then there's a single cell lining around that, inside of that pool noodle.

That's the gut epithelium. And its job is to keep all the bad stuff in and let the good stuff out into the rest of our body - the foam of the pool noodle, as it were. And so

that loss of diversity really, you cannot maintain that. The healthy gut barrier, that single cell lining is really disrupted.

And then you get leaky gut syndrome and that is associated with inflammation and autoimmune disease, risk of cancer and diabetes, and all these inflammatory chronic diseases that we're seeing. And we're seeing, steady increases in the numbers of these diseases and, and it's really related to our low fiber diet.

You said it. In the west we get half of the minimum. The minimum recommended amount of fiber is about 30 grams approximately, and on average, we're getting 10 to 15 grams in our diet in the west. Ideally even more than 30, you know, 70 to a hundred would be even better. But that lack of fiber really affects that gut diversity of microbes.

And then in turn, that leads to this loss of integrity of the barrier of our gut epithelium. And it's, it's a big problem and it really impacts our health. Tell me a little bit more about how that might predispose us to developing cancer. I think that was one of your areas of research, so I'd really like to hear more about what you have to say about how that increases our risk.

Dr. Vargas: Yeah. I love that. And again, just going back to the integrity of the gut, right - it's all dependent on lifestyle, food, the diversity of your microbes. And that dysbiosis or that imbalance oftentimes leads to increased inflammatory mechanisms which drive diseases like cancer, cardiovascular disease, uh, diabetes. And so, one of the studies I want to point out and this was groundbreaking research. What these scientists did was they wanted to study a cytokine. Cytokines are often immunomodulatory. And what that means is, if there is an inflammation or an attack or a pathogen, the immune system is going to release these cytokines. And one example of the cytokine is interleukin six. Interleukin six is called a pro-inflammatory protein. And what they did was they gave these mice a low-fat diet and a high fat diet. And they basically knocked out interleukin six. They got rid of the gene. So, the gene isn't expressed, it's not in this mouse anymore. We can forget about the cytokine. Well, they gave these mice their diets, and lo and behold, they found out that by just knocking out the cytokine, it lowered induction of liver cancer. And so, when you compare that with, let's say the intact interleukin six cytokine and the high fat diet mice, these mice were inundated with tumors on their liver. And so, what basically this, this is that obesity promotes liver cancers by this cytokine that promotes inflammation. And we know now that inflammation

is one of the main drivers of the progression and development of cancers, including liver cancers.

Dr. Black: That's so relevant. my listeners will recognize that I've said multiple times: One of the things I'm really concerned about in my patients is how often I am seeing elevations in liver enzymes in young teens. We're talking 12, year olds who are already showing inflammation in their liver.

And so, I, I really am concerned. 20, 30 years from now, I just think we're going to have an epidemic of liver cancer. And you just illustrated it goes back to the gut microbiome. They're communicating so, the bacteria and the gut are having a direct effect on whether or not our immune system is releasing these pro-inflammatory cytokines like IL six.

And then when we have higher levels of that, when we have a high fat or high ultra-processed food diet that damages our gut microbiome, our immune system is in turn making more of this inflammatory cytokine that then is, you know, we have evidence to show that that's having a direct impact on the rates of liver cancer development. So fascinating.

Dr. Vargas: Yeah. And that's scary because we've always thought of cancers, whether it's prostate cancer, breast cancer, liver cancer, pancreatic cancer as aging diseases. The number one risk of cancer is age. But you know, we're talking about inflammatory mechanisms that drive these diseases.

Dr. Black: It's well established, that people who eat a high fiber plant predominant diet have drastically reduced rates of colon cancer. Short chain, fatty acids, especially butyrate, suppress tumor growth through several mechanisms that we're just now beginning to understand. When given to cancer patients as a medication, sodium butyrate has been shown to increase the effectiveness of chemotherapy. Short chain, fatty acids have also been shown to be important modulators of cancers of other organs, including cancers of the cervix lungs, breast, bladder, liver, and prostate.

MD Anderson cancer center in Houston is doing some really interesting research on the skin cancer melanoma. One of the most difficult to treat and deadly types of cancer. They noticed that when melanoma patients receive antibiotics, the effectiveness of their chemotherapy is reduced. But when they gave those patients

fecal transplants and replaced those good bacteria, the patients responded better to their chemotherapy.

Dr. Vargas: Not only cancer, but to kind of go back to those cytokines that I was talking about. There was another example cytokine that is also a pro-inflammatory protein, called tumor necrosis factor alpha. And they did a study on mice as well, and they knocked out this tumor necrosis factor alpha in old mice. And they saw that the old mice had guts that mimic young mice. Yes, we need these cytokines that are released by the immune system. This is what alerts, this is what drives inflammation. And we need inflammation because it tells us, okay, we're sick. But if it's chronic inflammation, this oftentimes leads to many diseases and it's very hard to control chronic inflammatory mechanisms.

Dr. Black: That's an important distinction that I, I haven't discussed previously. So acute or short-term inflammation, when you're injured or sick, that's how your body - your immune system - helps you heal and recover from something that's assaulting your body, right? Whether that's a flu virus or you cut yourself broke a bone, you know, we need inflammation to help us heal and recover from these things.

On the other hand, chronic stress is when your body thinks it's constantly being attacked, but it's not. You know, our poor diets, our lack of sleep, our lack of exercise, smoking, excess alcohol, all these things affect our immune system so that it thinks it's being attacked constantly on an ongoing basis. And that's chronic inflammation and that's what strongly linked to all of these issues.

The evidence is very strong that you can prevent cardiovascular disease and diabetes with a high fiber plant centric diet. In fact, studies show that by increasing the amount of fiber in your diet by just five grams a day, you can improve your survival rate by as much as 30%. That's incredible. You can get five grams of fiber in half a cup of oatmeal or less than half a cup of beans, even a single apple has almost five grams of fiber. Maybe there really is something to that saying that an apple a day keeps the doctor away.

Insoluble fiber from the diet binds fat and cholesterol, thereby preventing its absorption. Soluble fiber on the other hand, feeds the bacteria that make the short chain fatty acids. And those can lower cholesterol levels by not only increasing their excretion, meaning you get rid of more of them, but also by preventing the liver from producing cholesterol in the first place. On the other hand, metabolites

like trimethylamine, which has made by the types of bacteria that predominate, when we eat a diet high in meat have been shown to increase the risk of developing heart disease.

The medical community has always focused on the treatment of heart disease and diabetes separately, considering only how to control the blood sugar in diabetics or lower cholesterol in people with heart disease. However, we know that the root causes of both of these is the same unhealthy habits, including our Western high fat processed diet.

Studies have shown that both type two diabetes and even advanced cardiovascular disease can be reversed. That's right - not just controlled, but actually reversed - with a whole food plant-based diet.

The most compelling evidence for this comes from Dr. Dean Ornish's pivotal Lifestyle Heart Trial. He randomized patients with moderate to severe heart disease to receive either an intensive lifestyle intervention that included a vegetarian diet or the usual standard of care for heart disease recommended by the American heart association. At the end of the study, the amount of blockage in the artery, supplying blood to the heart muscle (that's the coronary arteries) was significantly improved in the lifestyle group. Whereas the standard care group had worsening of their coronary artery disease and twice as many heart attacks than what was seen in the lifestyle intervention group.

Most of what we know about the effects of short chain fatty acids on diabetes relates to type two diabetes, where we're making plenty of insulin, but your body is resistant to it so it can't do its job to keep the blood sugar levels normal. In studies, fecal transplants have been shown to boost insulin sensitivity, even in just six weeks.

The other type of diabetes- type one diabetes- occurs when the cells in the pancreas that secrete insulin are destroyed, often by an auto-immune attack.

So, you're no longer able to make insulin in the first place. Here's where it gets really interesting. Recent research showed that in newly diagnosed type 1 diabetics, the butyrate produced by the healthy bacteria from a fecal transplant actually protected the pancreas cells and slowed down their destruction. It slowed the progression of the type one diabetes. That's incredible.

There are other ways that short chain fatty acids can prevent or alleviate type two diabetes. Maybe you've heard of the new obesity drugs like Ozempic. These drugs mimic the effects of a hormone secreted by the brain that tells us when we're full so we don't overeat. It turns out that short chain fatty acids travel from the gut to the brain and stimulate the production of these very hormones, thereby reducing your appetite. Maintaining a healthy weight is important because increased fat accumulation inside your cells is one of the main factors contributing to insulin resistance and type two diabetes.

So, on the one hand, our bacteria can significantly prolong our life by helping to prevent these killer diseases like heart disease and diabetes. But did you know that they may also actually slow the rate of aging?

The types of bacteria in our gut change as we age and interestingly scientists can guess your age with surprising accuracy by analyzing a stool sample. They look at your poop and they know how old you are. Dr. Vargas. And I talked about links between our gut bacteria and longevity.

Dr. Black: An interesting study looked at the microbiome of inhabitants in the blue zones, right? Those areas of the world where people live decades longer than other areas. And when they, when they took the gut bacteria and did a fecal transplant into mice, the mice lived longer.

So, it's not just the healthy -you know, they talk about a lot of other things going on in the blue zones in terms of social connection and the quality of their diet, and they tend to live in areas where they can walk more and get more exercise. And I'm sure that that absolutely contributes to their longer lifespan.

But just the bacteria themselves, when transplanted into mice, caused the mice to live longer lives. It's, it's really so fascinating how, you know, complex the interactions are.

Dr. Vargas: It is, and I'm glad you brought up the Blue Zones, because this goes back to aging and how aging guts have a high prevalence of dysbiosis. Meaning that they're losing a lot of their good bacteria. There are many gut microbe studies that attribute age with associated inflammation. And so, a lot of the diets that populations in these Blue Zones eat have the high fiber intake. They have a very diverse range of those microbes. And like I mentioned before in the age associated inflammation in mice, it's the cytokines like tumor necrosis factor. How you get rid

of that: you get rid of the dysbiosis. But again, we need our tumor necrosis factor. We need that to function. So, we need to maintain that healthy lifestyle and that healthy diet. Anytime you have increase of this proinflammatory cytokine, it's been shown to have increase in insulin resistance, diabetes, obesity, sepsis. And so, all of these are indicative of aging guts.

Dr. Black: We know that one of the important things that the gut microbes and the short chain fatty acids that they release does, is to help tame our response to sugar (glucose in our meal), right? It helps to even out our blood sugar response and the insulin secretion, and that's really important in our metabolism, how we use energy, preventing diabetes. I understand from a previous conversation that there's a relationship between insulin and something called insulin-like growth factor 1 and its effect on aging. Can you tell me a little bit more about that relationship?

Dr. Vargas: Yeah, this is, this is a very cool study; this is one of the most iconic studies that Cynthia Kenyon did a long time ago, and she did this study in worms, *C. elegans*. What she found was that insulin is actually the very first longevity pathway that was discovered.

There are numerous longevity pathways, but the insulin or IGF-1 is the main one. But this pathway basically showed in these worms tha, with calorie restriction you can extend longevity. They recapitulated these studies in mice and sure enough we have these same proteins that they saw in these different of animal models. It shows that, again, restricting or guiding that pathway and insulin we can increase longevity.

Dr. Black: I've seen two statistics recently. One is that it's been estimated that if you increase your intake of fruits and vegetables, if you get those five servings per day that are standardly recommended in our diet, you can add up to four years on your life expectancy.

That's just five servings of fruits or vegetables per day equals four extra years of life. But I, I also came across something that you know… in our society we are really focused on protein.

In particular protein from animal sources. And it's a common question that I get, "if we're eating a plant-based diet, how do we get enough protein?" But one of the factors when you look at the research that promotes longevity is actually a protein restricted diet. We are getting too much protein and it's actually hurting us. And it,

it was a strong scientific finding. I believe it's in Dr. Michael Gregor's book. He talks about it in *How Not to Age*. He just released that book at the beginning of December 23 - super fascinating and based on ridiculous amounts of research.

And, and that's where I heard this: one of the findings and when he reviewed the research is protein restriction actually equals a longer life. And, and it just, I feel like it has to go back to the microbiome because the organisms that we support when we eat a diet high in animal protein, which is low in fiber, fiber, is not found in animals, is going to promote the growth of those pro-inflammatory species of, of gut microbes versus the fruits, vegetables, beans, high fiber foods that promotes the healthy species.

And so, you look at it all together you're going to prolong your life by focusing on more of a plant-based diet and high fiber diet to help maintain that healthy balance of the pro-inflammatory versus an anti-inflammatory species.

Dr. Vargas: You mentioned the paleo diet and the reason why it didn't work was because they were eating too much meat. They were eating too much of the wrong thing this goes back to eating your fiber and main, making sure that you maintain that for your G.M. But again, very, very important.

Dr. Black: I promised at the start that we would talk about some simple things that you can do to keep your tortoise healthy. And we'll get there. I promise. But just to give you even more motivation, let's do a rapid-fire review of a few of the other ways that your gut microbiome affects your health. We talked about diabetes and heart disease, but what about the brain? The gut is called your second brain for a reason. The enteric nervous system and enteric is just another word for GI tract. Has over a hundred million nerve cells.

The gut brain axis is a back-and-forth communication system between the gut and the brain and emerging research suggests that the microbiome plays a crucial role in this communication. To begin with, did you know that over 90% of the body's neurotransmitters are produced in the gut? Neurotransmitters are things like serotonin (the happy chemical) and dopamine, which is involved in the reward center of the brain and is the reason you're addicted to social media.

Differences in gut microbiome composition have been reported between people with and without depression. Studies have shown significantly lower levels of acetate and propionate in the stools of depressed women. And there are case

reports where people with severe depression and bipolar disorder were effectively cured with a fecal transplant. Additionally - this is crazy- when scientists transplanted feces from people with alcohol addiction into mice, the mice developed alcohol cravings. Whereas a fecal transplant from a healthy individual into someone addicted to alcohol, reduced their alcohol cravings.

What about autism? Autism is a complex disorder, and we really don't fully understand its causes or the best way to treat it.

But there are some interesting studies suggesting that the microbiome is one piece of the autism puzzle. For example, when pregnant mice were fed a diet high in ultra-processed foods, they produced offspring with autism spectrum like behaviors. Another study noted significant differences in the microbiome composition of children with autism spectrum disorder compared to neuro-typical controls.

And the authors noted that there was a decrease in the synthesis of several neurotransmitters in the children with autism compared with the neuro-typical children. There are even studies showing a correlation between dysbiosis and autism symptoms and some children with autism had an improvement in their symptoms following a fecal transplant. This may be related to the effect of the short chain fatty acid butyrate on gene expression. More research is definitely needed to sort all this out. There's mounting evidence that short chain fatty acids play a big role in the prevention of Alzheimer's and studies are currently underway to figure out if we can effectively prevent or even treat these devastating diseases.

The microbiome even affects the quality of your sleep. Studies have shown that the more diverse your gut microbiome is the better you sleep. In another study, seven- to eight-month-old babies with higher levels of propionate in their stool had longer periods of uninterrupted sleep.

Let's talk about the immune system. This one really deserves an entire episode all by itself because the immune system and the microbiome are so closely connected, I'm sure I'll do one in the future. 70% of the cells in our immune system exists along our colon and they're crucial for fighting infection and recognizing and destroying cancer cells before they can start multiplying.

The gut microbiota communicates with the immune system via short chain fatty acids. They tell your immune system to turn down the production of the cytokines

involved in inflammation and turn up the production of anti-inflammatory cytokines. When I was in medical school, one of my professors referred to the pro-inflammatory cytokines as evil humors. If you know anything about history, you know that back before the germ theory of disease, people used to attribute illness to evil humors. Maybe they weren't so far off.

The health of your microbiome directly affects how susceptible you are to infections. While I was creating this episode an article was released indicating that vegetarians have a lower risk of coming down with COVID. Another study looked at the diets of healthcare workers during the shutdown. Nurses who were following a plant-based diet had a 73% lower risk of severe COVID versus the nurses doing keto, which is usually high in animal products and low in fiber. Those nurses had a fourfold, increased risk of dying from COVID. This is postulated to be related to the anti-inflammatory effects of the short chain fatty acids. There's also evidence that eating more plant-based foods can reduce the symptoms of long COVID.

What about when our immune system goes haywire causing allergies and asthma. Be sure to listen to episode 14. When I talk about food allergies and intolerance.

So, scientists studied the microbiomes of children who have food allergies and respiratory allergies like pollen, animal dander, things like that. They compared them to children without allergies, and they discovered that the allergic children's guts had fewer of the microbes that ferment fiber and more of those pro-inflammatory species. This was further supported by findings that allergic children have lower butyrate and propionate levels in their stool and higher levels of the inflammatory cytokines. Those evil humors.

Over the past few decades, we've seen alarming increases in the rates of allergic disease and asthma. And it really begs the question. Could this at least in part, be attributed to the increased availability of ultra-processed foods and the effect that they have on our gut microbiome?

It just blows my mind to think about all the ways that our microbiome effects our health. It can be thought of as another organ, just like your heart lungs or kidneys. And it's just as vital to the functioning of your body. So, what can you do to cultivate a healthy, diverse population of beneficial bacteria? I guess you could go out and find a healthy person willing to give you some of their poop for a homemade fecal transplant. Or you could just follow these eight simple tips.

Number one. Reduce ultra-processed foods as much as possible. Avoid pre-packaged foods with a long ingredient list that don't resemble anything you find in nature.

Number two, reduce red meat consumption and especially processed meats. Yes, I know. Bacon tastes great. But it's just not worth the increased cancer risk.

Three. Only take antibiotics for serious bacterial infections diagnosed by your doctor. Avoid taking them for common colds or other viral infections.

Four. Drink, plenty of water, green tea, and coffee. Yes! Coffee has been shown to be beneficial for the gut microbiome. Same goes for tea.

Five. Eat a wide variety of whole plant foods. Shoot for about 30 different plants per week in your diet. It's not as hard as it sounds. I'll include a link in the show notes to my breakfast smoothie, which has at least 10 different plant-based ingredients alone. Diversity in your diet is key. There are thousands of different variations of fiber in the plant world and, just like humans, different bacteria like different types of food. Aside from the fiber, the bright colors in different fruits and vegetables come from compounds called polyphenols, which also support those good bugs. Last some plants like potatoes and beans have something called resistant starch, which acts like fiber to feed your bacteria. Yes, potatoes can be healthy. Just not in French fry form.

Six. Consider practicing time restricted eating. This is a form of intermittent fasting. Some of the bacteria in your gut aren't there to help you digest your food. They're there to clean up the mess at the end of the day, clearing away toxins and other debris. They're like your own personal crew of night janitors and they can't do your job if you keep trashing your office all night long with a midnight snack. Shoot for a 12-to-14-hour window without eating or drinking anything except water, black coffee, or unsweetened tea. For example, finish eating for the day by around 6:00, sleep from about 10:00 PM to 6:00 AM, and then don't eat breakfast until 7:00 AM. Of course, you can shift these times to suit your own schedule, but you get the idea.

That seven to eight hours of sleep will also help your microbiome. Did you know that your bacteria also needs sleep? Changes in the gut microbiome have been seen. With as little as a single night of sleep deprivation. So, eat an early dinner

and don't stay up all night watching cat videos on Tik Tok. Both you and your gut microbiome will wake up refreshed the next morning.

Seven. Get regular exercise. Studies have shown that exercise can boost the population of beneficial short chain fatty acid-producing species in the gut. Just one more reason to get off the couch and lace up those sneakers.

Eight. Last, spend time in nature. Garden, hike, go fishing, or go to the park, play in the dirt. Studies have shown that people who like to garden have lower rates of depression. Now this could be attributable to getting out in the sun and the fresh air, the physical activity, or the satisfaction of growing your own food or flowers. But studies have also shown improvements in the health of the gut microbiome when people regularly put their hands in the soil. So, not only do you benefit from the act of gardening, you get to eat the fresh produce you grow, further enhancing your gut health. Win win.

We covered a lot in this episode. I am super grateful to Dr. Vargas for taking the time to share her knowledge about the fascinating interplay between our gut bacteria and our health. We learned about the GI tract and what a microbiome is. We reviewed the history of the discovery of the amazing community of microscopic organisms living in your gut and discussed many of the amazing ways those bacteria and the short chain fatty acids they produce affect almost every aspect of our health. Last I left you with some easy ways to improve your gut health. The important thing is to gradually develop healthy habits that can be sustained over time.

It's what we do most of the time that counts. Taking a probiotic supplement when you're on an antibiotic has a pretty minimal and a brief effect on the gut microbiome. There just isn't a one-and-done quick fix for your health. The interplay between your diet, healthy lifestyle habits, and the health of your gut microbiome is dynamic: It's ever changing. Just like you can't go to the gym one time and expect to have a long-lasting impact on your strength, you have to regularly eat foods that support the gut microbiome to effect long lasting change. Now that you have a greater appreciation for all of the ways that your gut microbiome affects your health, try to do whatever you can as often as possible to keep it healthy.

Thanks for listening and don't forget to… feed your tortoise! You thought I was going to say eat your greens.

