# Paleo Solution - 236

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Robb: Hi folks. This is Robb Wolf with another addition of the PaleoSolution podcast. Today I have a guest whose curriculum vitae I could spend the hour covering so I'll just do a very short treatment of that. We have Doctor Martin blazer who's the director of the NYU Human Microbiome Program. He's the former chair of the department of medicine and professor of microbiology at New York University School of Medicine.

Dr. Blazer also recently published the book Missing Microbes, How the Overuse of Antibiotics is Fueling Our Modern Plagues. Doc, a huge honor to have you on the show.

Martin: My great pleasure.

Robb: You know, I get a lot of questions from folks who are trying to figure out a career path in frequently medicine related, research related, could you maybe give folks a little bit of your background? And you went to medical school. Why did you choose microbiology and kind of an epidemiological kind of orientation? I think that's really helpful for people to understand why some folks who've just reached the pinnacle of success in a particular area – what drove you in that direction?

Martin: Well thank you. I appreciate that. I sometimes talk about it and I can summarize my career trajectory in one word. Accident. And that's kind of important for people to understand especially young people that there is no script. Things happen and in my case, I went to medical school. My goal was to become a doctor. When I was in my last year of medical school, I did research. It was completely a failure and I was sure that I was never going to be involved in research in my career.

But then I began my clinical training. I loved being a doctor. I started training in a specialty infectious diseases and I discussed it in missing microbes. I had a patient who had a complex problem and I thought maybe I can try to solve this and now 37 years later, I'm still at it.

Robb: It's funny. A lot of the self-help gurus will kind of paint this picture that you need to have this multi-decade plan and all of this clarity about what your next step is and what not but I found my own life as a little bit more like skiing through trees and just trying not to do a sunny bono on one of the trees. So I like your description of accident more than design.

Martin: Yeah. I mean on the other hand, if you want to be successful in this country and I consider this one of the greatest if not the greatest country, you have to work at it. You have to really work hard and you have to work with good people and find good people and learn how to work and play well with others just like our kindergarten report card said. And all those things turned out to matter. So you have to have hard work. You have to be lucky and you have to keep plugging away.

Robb: I like it. A little bit of my background, I was doing some research related gluten sensitivity, autoimmunity and what not and a good friend of mine who was at the Department of Pathobiology at the University of Washington. She and I were talking and she said you know, this gluten stuff is really, really interesting. You're really on to something here.

But she said really at the end of the day, this is all going to boil down to bacteria and microbes and infectious disease and I was like no, that's crazy talk. This gluten thing, evolutionary biology, caveman diet, that's really where it's at and then ironically she was 100% correct and I looked back.

Martin: Well you know they all interact. As a microbiologist obviously I think microbes are important and we're dealing microbes across the whole mainstream of medical science in a much more broad way these days. But microbes aren't everything but they certainly are a lot and I'm happy to talk about it.

Robb: You know, it's interesting. It definitely seems like peeling an onion where you know, at one point we were just talking about endocrinology and then some elements of immunology then eventually we started getting into genetics particularly with the human genome project and then we started getting into proteomics. But I think that the explosion of an understanding of this kind of endosymbiotic relationship between microbes and our gut health and our external health, this antagonistic or

beneficial relationship with microbes is really blowing the doors on a lot of areas of medicine.

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And introduces to me a layer of complexity that is just kind of staggering when you look at the gene transfer between microbes and then how that may interface with our own genome and our own proteome. It's pretty amazing the level of complexity there.

Martin: A lot of complexity and it's really based on the fact that we have been living together with microbes, coexisting in the same space as long as there have been animals on this planet which goes back at least 500 million years. There have been residential microbes in and on animals such as all of our ancestors. And as a result, they've learned to live with us and we've learned to live with them and it has been mutually beneficial. That's most of the story of human microbiology.

And the other part of the story is about the pathogens, the ebolas, the influenzas, the plague, those organisms, those are important too but those are much less frequent. And in fact, the good guys help us fight against the bad guys.

Robb: And you know, I have some questions later kind of talking about that like the Nash equilibrium and some things like that but augering in maybe a little more specifically to your research background, what drew you the H pylori? Why was that just a hot topic for you or how did that get on your radar?

Martin: Well it's again, accident. If you remember in Missing Microbes, I talk about that first patient who really got me interested in trying to solve problems. He had an infection due to a weird organism called campylobacter, an organism that I have never heard of. But I started researching his case. I started studying it. I started doing research in campylobacter which as a bacteria of the gastrointestinal tract and it turned out it was a major cause of diarrhea.

One of the main causes of diarrheal illness all over the world, more common for example than salmonella which most people have heard of. So I was working on campylobacter quite busily and then one day a new

campylobacter was discovered in the summer and it was called gastric campylobacter like organism. And that got my attention.

And over the next six months or a year, it became clear that this organism was playing a role in ulcers. And along the way, the microbiologist started looking at these organisms and they changed the name from gastric-campylobacter-like-organism to campylobacter pyloridis. And then to campylobacter pylori and finally to helicobacter pylori. So it was discovered as campylobacter in a field that I was already in so I just stepped across and said let's use some of the same techniques we're using on campylobacter to study this new campylobacter. Back to our first publications, it's called campylobacter.

Robb: Interesting. And I know that when it was first posted that H pylori could be a factor in gastrointestinal illness and ulcers that this was a very controversial suggestion and it was not well received by the mainstream medical community and there was actually a little bit of acrobatics to bring that to the forefront.

Martin: Well just as you say, the medical field like many other fields has its dogma and the dogma was that ulcers are due to acid, stomach acid and to stress. But the work of Marshall and Warren showed that these bacteria that live in the stomach are very important in the causation of ulcer disease.

And ultimately to make a long story short, we now accept that this is correct and Marshall and Warren actually won the Nobel Prize in medicine for their discovery of this organism and its relationship to ulcer disease. And they were the leaders in that field. I was involved in the work but then we showed that the bacteria was very important in causing stomach cancer which stomach cancer is the number 2 cause of cancer death in the world.

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So helicobacter pylori as it was then called or H pylori or HP as we call it for short was on its way to being one of those bad organisms, one of those – the ebola of the stomach as it were. But then we started studying it some more and some things didn't quite fit because lots of people have helicobacter. People have it in their stomach for years and decades and they don't have any symptoms at all. They're not ill. And we begin to find

that helicobacter is actually very old in the human stomach, as far back as we can trace human ancestry.

We found evidence of helicobacter and now there's evidence taking it back at least 200,000 years. This organism's been with us for a very long time and then we begin to find evidence that helicobacter has a dark side. It increases the risk of ulcers. It increases the risk of stomach cancer but it has a light side. It decreases the risk of other diseases like esophageal reflux and some of the problems that come about after reflux which is also called GERD.

And suddenly the picture became more complex. The organism was bad for us. The organism was good for us and we've been working on both sides now for more than 20 years and interestingly the mainstream medical community still hasn't come around this idea of the good side of the organism. I talk about it in the book. We and others have huge amounts of evidence that this bacteria has benefit. But most doctors in the world are still trying to kill it.

Robb: Doc, part of that story has a little bit to do with early versus late exposure. Is that correct?

Martin: No, it's more like early versus late consequence.

Robb: Okay.

Martin: Everybody who has it gets exposed early in life. And I mean you're jumping almost to the punch line which is that our view is that the bacteria turns out is good for us when we're kids. But it's bad for us when we get elderly. And in that sense, it's almost the perfect symbiotic. It keeps us alive when we're young. It helps us reproduce. And then when we're past reproductive age, it moves us toward the door.

Robb: So hopefully in some ways maybe a little antagonistic towards collecting the pension later, that's interesting. You know…

Martin: Say this whole idea about antagonistic late in life it turns out that's a perfect symbiote. Bad for the individual, bad for us to be knocked off but it's actually good for the species.

Robb: Right.

Martin: Nature's rules. The resources, food is always in short supply and nature conspires to knock off the old guys so that there's room for the young guy.

Robb: Right.

Martin: It's not my rule. That's a fundamental rule of nature and we have hypothesized that smart bacteria like helicobacter that have been with us for a long time actually have those two roles.

Robb: Follow that duel trajectory.

Martin: Exactly.

Robb: Interesting. You know, a lot of your work reminds me of Ignaz Semmelweis he was critical in establishing the germ theory of disease. Nobody really believed him at the time and then clearly very powerfully vindicated. Now we're kind of entering this hygiene theory of disease period. It's interesting at one point we were kind of focused on eradicating everything and I think this kind of ties into your book which I'll ask you more questions about the book later but now we're finding problems with this.

When overly hygienic environment, we're not really tuning the immune response to the degree that we want. You kind of alluded to this in your opening a bit I guess the vast majority of our microbiological interaction is actually beneficial. We get a few zingers every once in a while like a treponema pallidum or ebola or something like that. But for the most part, it seems to be beneficial.

But how are you seeing I guess maybe on the research front, the education front striking a balance between understanding clearly there are problems with infectious disease but at the same time we may be creating all kinds of other problems with increase rates of auto immunity, increase rates of certain types of cancer because we're not tuning that immune response throughout life.

Martin: Yeah. I mean again, this is why I wrote Missing Microbes. This is a very rich area and I've written a whole book just about that subtopic. It almost goes back to the history of early science in the 19th century. Pasteur, the Father of Microbiology felt that microbes were good for us, that they

were essential for life. But Mechnikov who was the Father of Immunology felt that microbes were antagonistic to us. They were bad for us.

And that kind of dichotomy has persisted to the present. In reality of course the answer is somewhere in the middle. It depends on context. It depends on developmental stage. It depends on so many different factors. So but the history of microbiology is the history of discovery of pathogens. What was the cause of cholera? What was the cause of tuberculosis?

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Now we know TB is caused by a bacterium but people didn't know that, that was a great discovery in the 19th century. And so the whole history of microbiology was the discovery of pathogens. And then with their discovery we had to prevent them and treat them and that's what lead to sanitation and the discovery and implementation of antibiotics. All of that was great. We improved human health a lot.

But what we didn't understand is some of the things that we were doing to get rid of the bad guys, the pathogens also were hurting our good guys. And that's kind of where we are today. Probably we people in the US have a very impacted microbiome. Not only are we messing up our macroecology with global warming and acid rain and others. But in essence we're doing the same thing inside our body. And that I believe has health consequences and that's really what our work, our research work is focused on.

Robb: You know I do some kind of philanthropic work with the Savory Institute. I'm not sure if you're familiar with them but they use a method of holistic livestock management to help reverse desertification in areas where desert is encroaching into normally a well healthy pasture land and one of the primary focuses that they have is actually reestablishing the soil microbiome diversity that the soil microbiology ends up becoming very, very rarified and then it's easy for that area to become damaged and difficult to reestablish grass lands.

So it's interesting when they go to some of the lectures that these folks put on. It's as if the grass lands that they're describing, it's almost the same story as our gut.

Martin: Yeah. This is the rules of ecology are the same whether you're talking about forests or grasslands or animal and populations or microbial populations. Ecology is ecology and we're finding great similarities. In fact, understanding about macroecology has been very helpful to me. But the bottom-line is that there's more and more evidence that we people and developed countries like the United States are losing our internal biodiversity. And as ecologists would tell us, that's a bad thing.

Robb: Right.

Martin: And I think we understand why we're losing it because of antibiotics and antisepsis and a number of other things, caesarian sections that have really changed the transfer of our normal microbes or the maintenance of our normal microbes. So we think we understand the general causes of it and we're now trying to come to grips with what are the consequences and that's our research work has largely focused on obesity which as you know is one of the big epidemics into the late 20th century into the 21st century.

Dramatic changes in the United States happening all over the world. So something really pretty vast must be happening to trigger this. Also it's happened very fast. Huge increases in obesity has been really in the last 30 years. That's like the second in human evolution. Something very strong environmentally must be going on and of course our hypothesis is that it's this change in the microbiome. This loss of biodiversity in part driven by antibiotics.

Robb: Right.

Martin: The unintended collateral effect of all the antibiotics we're using.

Robb: And you know, I spent probably a good 10 years of research kind of looking at the protein carbohydrate fat debate as to whether or not you know, insulinogenic foods were the cause of obesity and what not and it kind of fit the data a little bit but not really in other pieces. And I've got to say as I've learned more about the gut biome and systemic inflammation that can extend from that scenario the alteration of the gut biome definitely seems to fit that data rather nicely.

But it's almost painful in a way because it creates a layer of complexity again that is daunting to try to figure out what the heck we're going to do about it.

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Martin: Yeah. There's a lot of complexity but the general principles are pretty straight forward. Let me tell you about three studies. First, our studies that were done in the 1940's and 1950's by farmers who found that if they fed low doses of antibiotics, that would make their animals get bigger. That's what was called growth promotion. And it works. That's why farmers are using antibiotics on farms, to fatten up their farm animals. That's why 80% of the antibiotics used in the United States are used on the farm because it works.

About 10 years ago, all the sudden I got the question. I knew about this for a long time but the question popped up in my mind is why does it work? Why does giving antibiotics make the animals fatter and bigger? And as I was reading into it, I learned that the earlier in life they started the antibiotics the more profound the effect. And that suggested to me that it was developmental. There was something about our developing – firstly it suggested that it had to do with bacteria, with our microbiome. So that's the first studies. All the studies in the farm.

So then we did a study to see can we recapitulate this in mice? In the laboratory? Can we give them antibiotics and make them fatter? And the bottom-line is yes. We did that. We had a paper that was published two years ago in nature, a very extensive paper showing all the observations on the farm could be reabsorbed in the laboratory, in mice. We showed the microbiome was altered in its composition. We showed that it was altered in its metabolic activity.

We showed that the liver, the genes in the liver were altered because of what was going on in the gut and the mice were putting down more fat. So that really established the principle very clearly that giving antibiotics early in life could increase fatness.

And then we had a second study which was just published a couple of weeks ago in the journal cell and it's a very extensive paper. I can tell you about doing different parts of it. But I want to focus on one experiment that I think you'll find interesting and that is we did an experiment and

that was done by Lorry Cox, graduate student in the lab who's originally from California and Lorry did very extensive studies.

In this study, she gave mice antibiotics and they became fat. And then another group of mice, she put them on a high fat diet, high fat, high calorie. They became fat too. And a third group of mice got high fat diet and antibiotics together and they got very fat. And the control group of course didn't get fat. That's what we were comparing it to. So we showed both in male mice and female mice that a combination of a high fat diet and the antibiotics was additive and it was even more than additive. In the female mice, adding the antibiotics to their food doubled the amount of fat that they've put on.

Robb: Interesting.

Martin: Had a huge effect.

Robb: Doc, my understanding of a lot of that is that some of that is a lipopolysaccharide driven inflammation that alters kind of liver pathology and liver processing, creates some systemic inflammation. I have seen some work that suggests that a very low carbohydrate diet like a ketogenic diet is so low on carbohydrate that it actually ends up pruning back some of the biome which actually long term may actually end up being problematic with ketogenic diet.

Do you have any thoughts on that because frequently these high fat diets are – when they're studied, they still have enough carbohydrate load, enough resistance starch load that we can keep the gut biome scooting along where sometimes if we introduce a very low carbohydrate level, we end up pruning back the gut microbiota and so even though we get a greater translocation of this LPS into the system and potentially some inflammation overall we have less LPS being produced because of a smaller bacteria population.

Martin: Yeah. You know, the first thing to say is the LPS is a theory and it's an interesting theory and there's evidence that's supporting it but I want to get back to the biology and that is to remind you and your listeners that the gut microbiota is extremely complex. There are hundreds of different species all of them competing for food. The food that you eat, some of it goes to us and some of it goes to them.

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And when you change diet, it has a big effect on the microbiota and the kinds of bacteria that produce this lipopolysaccharide or LPS or what I call gram negative bacteria, there are so many different species of gram negative. When you change the diet, you will increase some of them and you will decrease others. There's no simple relationship. It's not carbohydrates mean more gram negatives. The protein means more affirmatives there. There are organisms in both groups that go up or down with relation to diet.

So I don't know. Obviously when you change diet, you're going to change microbial populations but there has been not been a clear and a consistent pathway that helps us understand certainly we know that when you reduce calories, people lose weight. But we don't exactly understand what's happening microbiologically.

We're actually working with some colleagues who have done an experiment with very overweight older women, giving them a diet that has caused them to lose 10% of their body weight. And we're now studying their microbes. We're finding some general trends but right now it's at an early stage.

Robb: Doc are you able to share kind of the details of what that dietary intervention is and compositionally?

Martin: You know, I'm not an expert in this area but the basic ingredient in the diet is that it's very low calorie, severe calorie restriction and people can lose weight off calorie restriction. We know it is very difficult to do.

Robb: Right. Yeah. Difficult to keep them on that. So probably I would be surprised if you have not followed Jeff Leach's work at the Human Food Project?

Martin: Well we're actually working with Jeff. In fact, we visited him in Tanzania just a few weeks ago.

Robb: I had an invite to go out there but we just had my second daughter about a month ago and so I had to pass up on it. This year I'm trying to bend the wife's ear to let me do it next year. Tell folks about some of that work please.

Martin: Well Jeff has been studying a group of people in Tanzania called the Hadza and this is a group of hunter-gatherers. These are people who the men shoot their game with bow and arrow. The women gather wild honey. They dig tubers out of the ground. They've been living this way for 50,000 years maybe longer. They're very ancestral population African.

Jeff decided that he wanted to study them and he's been getting specimens of their microbiome, some of them are in our lab here in New York, my wife Maria Gloria Dominguez has been working with Jeff for the last year and we've actually begun to do some actual studies for our learning sequences.

But the thing that was so surprising to me when we went there a few weeks ago is how rapidly things are changing. We saw hunter-gatherers just like they've been for thousands of years but in one of the camps somebody had a cellphone. The question is where did they get electricity for the cellphone and who are they calling? Somebody had a cellphone.

So progress is everywhere even in very developing areas of Africa. We've seen that in the Amazon as well. People want a better life and if you could get a big sack of corn and you don't have to hunt and dig up tubers for five hours a day, people go for that. So we want to study these people as rapidly as we can before their way of life has changed completely.

Robb: Right. Do you have any sense of are we going to be able to create some therapeutics based off of some of those profiles to be able to help our current westernized population? Is it going to be a combination of maybe customized microbiome what sequences are mixed? And then also I guess another piece of this, how important do you feel it is to get people eating something that looks more kind to lower process the ancestral diet, to make all of that stick?

Martin: I guess the first thing to say is yes, the hope is by understanding what ancient people had in their gut, we can compare with modern people and say aha, we seem to be missing something. Maybe we need to give that back. I discussed that in missing microbes and again my wife Maria Gloria Dominguez has been working on this concept for the last decade and we have specimens from the Amazon and now working with Jeff, specimens from Africa to try to answer exactly that question.

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And so we think that one day this will lead to actual probiotics that will be useful for people but it may be that your probiotic is different than mine. We don't know that yet. And then the other question is what about the diet? A diet is important but as we just discussed, it's complex and I think the idea of a healthy diet is ultimately the trump card, a balanced diet is unprocessed as possible because all the things we're doing to process food are removing nutrient value.

Robb: You know, one thing that I've kind of wrestled with when I looked at Richard Wrangham's work, his book Catching Fire and he makes the argument that a big step in human evolution was actually the utilization of fire to start cooking both animal and plant products which clearly that's going to change the types of bacteria that we interface with just by potentially sterilizing the food or partially sterilizing the food.

But it seems to run the gambit from you have some folks that are recommending a purely raw diet and trying to still get as much of the bacterial load that you would get out of the soil and what not. You have other folks who are recommending an incredibly well cooked palette because it's easier to digest. What are your thoughts on that? My gut sense is it's somewhere between and it's going to depend on the person but I mean what are your thoughts on that?

Martin: I don't have a strong opinion. I think there's a lot of research that has to be done to – you know what, for the last 20 years or 30 years there's been a lot of research on diet. Now we're saying that the relationship between the diet and the microbes is important. I think everybody accepts that that's a new frontier so we have to do the research to really answer the question we're posing.

Robb: Right.

Martin: And again the answer for me may not be identical for the answer for you.

Robb: Doc, with the way that randomized controlled trials are usually put together, is that going to lend itself really well to fairing out what's good for one person versus another? You know how – there are classic gold standard RCT – how is that going to be helpful for finding what's good for the individual? That's another perplexing element for me.

Martin: Yeah. You raise a good point. But the RCT, the Randomized Clinical Trial is a very powerful tool because bias is everywhere and anecdote is everywhere. And unless you do studies in an unbiased way you will be lead astray. The history of science is full of that and somebody says I did this and it was good for me, that, it has to be tested. That's the difference. That's the basis of science. You have to have a hypothesis and you have to have a rigorous way to test it. Otherwise you're just kidding yourself.

Robb: Right.

Martin: So from randomized trials, you can generate big principles, you can understand big kinds of things. And the better you understand how people differ within the trial, the better you can stratify it, then you can get to the next stage of knowledge. But it's incremental. And it takes time.

Robb: Right. Right. Doc, this gets out in the weeds a little bit but could you talk a little bit about the Nash equilibrium is a model for kind of the co-evolution of the humans and bacteria. My listeners are pretty savvy group and I just found that topic fascinating when I was reading both through research and your book. If you want to jump in on that, if you don't want to, we can just skip that one.

Martin: It's an interesting and complex idea and a number of years ago, I was commissioned to write a paper for nature. Again, with very high impact journal about our evolution with microbes. And I was looking for the whole issue of – well let's put it this way. In a typical Darwinian model, it's survival for the fittest. Dog eat dog, may the best dog win etc. It's a model of competition.

Yet if you look at the natural world, you see that there's cooperativity everywhere, all kinds, just like the cooperation between us and our microbes. So there's lots of evidence of cooperativity. So the question is how does that work? And I was Googling one day. I was looking at the internet and I came across this concept of a Nash equilibrium and I thought to myself this could help solve the problem.

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So John Nash was a mathematician. He worked at Princeton. They made a great movie about his life called a beautiful mind that many of people have seen because he was schizophrenic. Brilliant man but schizophrenic

and over the course of his life things basically improved. But out of his genius, he could see relationships that other people couldn't.

And what has been called the Nash equilibrium is a concept in game theory which says that Nash equilibrium is a state in which people – if the players in the game play by the rules, they will end up in a better position than if they cheat. So fair players win. Cheaters lose. And in a sense, that's almost antithetical to the Darwinian view which is cheaters win.

And so Nash equilibrium is a kind of special case. It turns out it's not against Darwin at all. It's just kind of a specialized problem with Darwinian evolution. But the whole way to understand cooperation is that you have to have, understand how you can control cheaters because once there are cheaters, cooperation stops.

And so our concept there was a Nash equilibrium exists let's say in the human body between us and our microbes and they have been – natural selection has favored microbes that don't want to kill us, that want to live happily with us and we want to live happily with them and that there are penalties against organisms and people who break the rules and that's part of our ancestry, part of our evolution.

Robb: Right.

Martin: That could help explain why we are coexisting with these organisms for the last 500 million years.

Robb: Doc, this really gets out in the weeds and is very speculative but could you maybe make an argument that just humans being humans and the Nash equilibrium kind of perspective we are kind of cheaters like we had this mega fauna die-off, we killed anything bigger than about 60 kilograms on virtually every continent and that's probably a little bit of a driver for the development of agriculture and then we were smart enough to really drive agriculture to a point where we had populations that could totally collapse ecosystems and now we have that whole story maybe played out on a global level.

So on the one hand you could say on the short term we've been cheating and winning but I think that you could maybe make an argument on the other side that there might be some pretty dire consequences for us in our co-inhabitants on the planet like does that kind of fit within maybe a

Nash equilibrium that we've been skewing things because we are really, really smart monkeys?

Martin: Sadly I agree with them. Sadly that's one of the implications is that you can cheat in the short term but you can't cheat in the long term. If the concept of the Nash equilibrium is correct as I've applied it in this situation, it means that there are going to be some long term consequences and in fact I talk about this in chapter 15 of the book which I call antibiotic winter which unfortunately is a very bleak scenario of a huge plague, huge pandemic kind of fueled by lots of the factors of modern life such as the fact that instead of living as hunter gatherers in tiny little villages disconnected from everybody.

Now we have a contiguous human population of 7 billion of people and the large population size selects for a different kind of microbial transmission. It selects for pathogens. Hunter-gatherers, it selects for symbiote.

Robb: Let's say at worse rate…

Martin: Right. So we live in a smaller world. On the other hand, many microbes are becoming antibiotic resistant because of our terrible overuse of antibiotics. And because of this loss of diversity that we keep coming back to, we're less well prepared for an invader than we were a century ago because the good guys help us defend against bad guys. But we've lost good guys.

So the point of talking about this is not to just scare everybody silly but say if there's going to be a bad plague that comes tomorrow we're out of luck. But if it's going to come 100 years from now then we better start trying to prepare. We better start to try to restore diversity and figure out ways that we can get back in that Nash equilibrium so that we can minimize our chances of a catastrophic effect.

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So what you were talking about is the fact that our populations are getting bigger. We're getting older. All that looks like we're outsmarting nature, remember, nature always wins in the end. And so the question is are we putting ourselves at risk for a catastrophic effect and the answer is

we may be and the catastrophe will be the pathogens. It will be a pathogen that arises, an ebola virus that can't be stop.

Robb: And is easily transmitted and all the rest of it ticks all those boxes.

Martin: That's right. As bad as ebola is, and it's terrible. It's not easily transmitted. So if ebola were transmitted the way influenza is, we would be in big, big trouble.

Robb: Right. I think maybe you just answered my next question which is why did you write Missing Microbes? Probably some serious anxiety about what course we're on but is that the main trust? Trying to create some awareness about misuse of antibiotics, the loss of overall gut diversity, maybe some mismatch of the way that we're interfacing with our ecology over the long term. Is that all of it? Was it more than that?

Martin: Well it's all of that and it seems – I can reduce it to a more practical level. And the practical level is a parent with a young child. The young child is running a fever. They have an earache, and now in the United States, the parent goes with the child to the doctor and the doctor examines the child and gives the child an antibiotic. And the parent is happy and the doctor is happy and that's all based on the idea that the antibiotic has benefit. Or if it doesn't have benefit, at least it doesn't have cost.

But what we know is that most of those infections aren't even caused by bacteria. It's caused by viruses. So the benefit in those cases is zero. And if there's still no cause then it's okay. But if we start thinking that there's a cause that every time we give a child an antibiotic, we're going to knock off a few of their organisms in their biodiversity then it begins to get serious.

And if every time a child takes an antibiotic, they have a few percent increase in the risk that they're going to get asthma or obesity or diabetes. Then, and it's cumulative, then really it's a different equation. And that's the main reason I wrote Missing Microbes. So people could understand for themselves what we're up against and making decisions for themselves.

One of the points I make is that in Sweden where the people are just as healthy as we are, maybe healthier, they're only using 40% of the antibiotics that we are. That immediately applies that 60% of the time the

antibiotics we're using are unnecessary. So I want to first stop the destruction and then we have to work on the reconstruction.

Robb: Doc, what about – you know, so even using fever controlling agents like ibuprofen and acetaminophen that are going to modify that inflammatory response clearly I have a 2 ½ year old daughter. I now have a month old daughter when they start running a fever, you get a little nervous. Convention would have it that if it starts going north of about 103, 104 then we probably want to do some sort of an intervention there. What type of modifications are we getting on long term immunity and tuning the immune response even with things like NSAIDs.

Martin: You know, bottom-line, we just don't know. The conventional wisdom is when a child has fever to give them something to reduce their temperature. But we know that increase in body temperature's a physiologic response to infections with lizards who are cold blooded animals and you can put them in cages of different temperatures, when you put them in a warm cage they do better than when you put them in a cold cage.

There are different kinds of experiments like that that show that fever has benefit. So again, short term child feels better. Long term we don't know.

Robb: We can probably make an argument that there's going to be a gain on that evolutionary trade off there might be something untoward waiting for us at the end of that. I mean we don't have data to support it but there's probably a good assumption.

**[0:45:00]**

Martin: That's the kind of stuff that really needs experimentation. We could study that in mice for example and probably learn very clearly what the story is for humans, for human children. Does damping down fever when a child has an early infection, is that ultimately going to be good for the child or bad for the child? We don't know the answer to that. It needs to be studied.

Robb: Right.

Martin: Because it's happening on a scale of hundreds of millions of times every week.

Robb: Well you know, even just with my daughter when we did the MMR vaccine, she ended up getting up to 104. She got a really potent response from the vaccination, the second go around on that and we're trying to mainly deal with that by doing cool water and it finally reached a point where it's getting us nervous enough that we did a little bit of children's Tylenol and brought that down but it's – I tell you, sometimes you're just a wash with information. You feel a little damned if you do and damned if you don't.

You're an irresponsible parent if you didn't administer that children's Tylenol but then if she ends up with asthma somewhere down the road do I look back and think wow I could've been short circuiting some of the immune tuning that she needed early in life as part of that whole process?

Martin: You raise very good questions. Bottom-line is we do not know and I wouldn't want parents to feel guilty one way or the other because we just don't know. Again there's been a conventional wisdom that such things are good but it's happening at such a scale that we have to find out. I think it's a very important research agenda especially for young kids because they're developing.

Robb: Right. Doc, if you had a couple of takeaways for folks they could enact, so if one of their kids were even adult listener they go to the doc, if there is an argument for taking some time if you are sick, trying to do some cultures to see if we have a bacterial versus a viral infection. What are some things that people can do to start getting some positive direction?

One thing that I work actively towards is trying to promote grass fed meat production which bypasses that utilization of antibiotics in the grain fed kind of confined feed lot scenario that's one area that I try to put a lot of time and bandwidth into. What are some other things that folks can do today that may benefit them?

Martin: Well I want to make the point and that again part of why I wrote missing microbes is that certain of the things that we take for granted have cost. Cost that we didn't realize before. Now when a child is really, really sick, they need antibiotics. There's no question about that. But there's a lot of gray zone. And that's why we have doctors. And the job of the doctor is to

figure out when should that child get an antibiotic? When is it absolutely necessary and when they don't need the antibiotic?

In the United States you need a prescription to get an antibiotic which I consider a very good thing. So it's really the parent shouldn't feel deprived if the doctor says I've done a careful exam. Your child – I don't think the child has a severe bacterial infection. Chances are this is going to go away in a day or two. Let's watch it carefully and if there are problems, come back. I want to try to change this scenario to be more like that. More like the Swedish model so that we're not abusing these very powerful drugs.

Robb: Great. Fantastic. Doc, did we miss anything? Anything else that you want to share with folks?

Martin: I'll just mention one thing which I mentioned very briefly and that's caesarian sections. We humans are mammals. For the last 100 million years, mammals have been giving birth by the baby being born essentially sterile and moving out through the mom's vagina into the world. And during that movement, the baby is acquiring microbes from their mom. That's part of the intergenerational transfer of microbes from moms to babies.

Well when a baby is born by C-section that doesn't happen and the work of my wife Maria Gloria and Rob Knight have shown that the microbiome of babies born by c section is different than babies born vaginally. And there's now more and more evidence that a hidden cause of C-section is increased risk of such things as type 1 diabetes and obesity and celiac disease.

So we're messing with the microbial world in ways that we didn't even imagine but it's happening and in the United States, one out of every three babies today is born by C-section. In Brazil, it's half the babies are born by c section. So this is kind of a medical procedure that's gone out of control. Everybody thinks it's free, the doctors, the patients, but it has cost and those costs have to be balanced against the benefit. In some of the advanced countries of Scandinavia, the rate of C-section is about 15%. So there's lots of room for improvement.

Robb: That's a controversial spicy meatball right there. That's a good one to leave off on. Yeah.

Martin: I discussed it in much more detail in Missing Microbes so that it's not just a sound bite.

Robb: Right. Dr. Blazer thank you so much for coming on the show. I know folks will love this. I love your work. I followed it for years. My progress through this has been largely from a kind a metabolism biochemistry kind of background and then have shifted the last maybe 5 or 6 years much more into the gut biome and trying to understand that interface with our health so it's a fascinating area of research.

Martin: Well thank you very much. A real pleasure to talk to you. You've asked all the right questions.

Robb: Thank you. Thank you. I'm glad I did that. I was pretty nervous for this one. You're kind of a hero of mine so I was a little nervous on this interview. So thank you so much and thank you for being on the show.

Martin: My great pleasure and I hope I'm helpful to all the good…

Robb: Incredibly helpful. Thank you for both you and your wife's work and Jeff Leach and all the other folks trying to peel onion and figure out what this part of our human evolutionary story is all about.

Martin: Yeah. Thanks a lot.

Robb: Thanks doc. Take care.

Martin: Bye.

Robb: Bye.

**[0:51:55] End of Audio**