March 2014 Issue | Patrice Cani, PhD Catholic University of Louvain

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Welcome to *Functional Medicine Update* for March 2014. Oh my word, do we have a wonderful March episode for all of you that really follows on from our extraordinary first two issues of the year 2014. Just to kind of recount and recap where we have come so far in 2014 and what has emerged to be a mini-course in what I call functional gastroenterology that is really pace setting in the 21st century of a systems biology approach to medicine.

You recall that in January we were very fortunate to be able to interview Dr. Alessio Fasano from Harvard, who arguably is one of the select group of people in the world that understands and is elucidating the effects of gluten in immunologically sensitive individuals and the role it plays in immunological activation and alteration. I believe that Dr. Fasano's interview really opened up the discussion of gluten and gluten-like protein molecules and their effect on the immune system in a way that was much more expansive than we had previously even thought of, moving it into areas of childhood development and things like autistic spectrum-like disorders, and discussing the effect on seizure disorders, and the effect on autoimmune disease in later-age individuals. These are all extraordinarily interesting emerging topics to come out of the gluten story, that's much more than celiac. In fact, he talked about non-celiac-related gluten sensitivities and the cooperative work among European gastroenterologists that have put together a position paper illustrating the importance of this topic in medicine.

From Dr. Fasano's extraordinary discussion we then moved into the second of the three parts of this mini-course, which was Dr. Gasbarrini—again, arguably one of the world's renowned gastroenterologists and certainly a leader at the University of Rome, School of Medicine. He has published over 400 papers on a broad range of activities and discoveries. His focus was on gut permeability, you might recall (or "leaky gut"), which we discussed as being considered an artifact term when it was first used some 25 years ago in *Functional Medicine Update*. People thought, what the heck is 'leaky gut syndrome'? You know, it was pretty much a term that was considered artifactual to good gastroenterological knowledge. But over the past two-and-a-half decades, this term has become much more frequently used and, in fact, if you do a PubMed search now under the term "leaky gut" you'll come up with a variety of high grade publications, some of which have come out of Dr. Gasbarrini's laboratory itself.

Dr. Gasbarrini helped us to understand the tight junction physiology of the gut mucosal cells. He helped us understand the goblet cell activities and these intercellular junctions which then become permeable to larger molecular weight molecules and how that activates the immune system and can induce systemic inflammation. Therefore I thought Dr. Gasbarrini, who is really a very traditionally focused and trained

gastroenterologist who has undergone this conversion experience in his understanding of the role of the gut immune system and the influence that diet and microbes have on gut permeability and gut mucosal integrity, has really reflected the change in the field in general. So that was an extraordinary chapter 2 in our three-phase discussion as to how the gut influences systemic health.

And that leads us to this issue this month with Dr. Patrice Cani. You might recall (those of you who have been long term *Functional Medicine Update* subscribers), we had the privilege of visiting with him and his colleague, Dr. Nathalie Delzenne, at Catholic University in Louvain in Belgium, in which he and Dr. Delzenne described their earlier work as it pertained to the gut microbiome and its interrelationship with immune function—the so-called gastrointestinal associated lymphoid tissue (GALT) of the gut and how that influences systemic immune system function. Much has occurred, as we'll hear from Dr. Cani, since our interview with he and Dr. Delzenne some years ago. In fact, nearly a hundred publications later, over these but few years, illustrates his productivity out of their laboratory in the Metabolism and Nutrition section at Louvain.

This is, I think, a very remarkable time of change. And what you'll hear from Dr. Cani in his discussion with me is the emerging understanding of the outcome that occurs from the leaky gut and from gut inflammatory processes that may be associated with things like gluten and other perceived foreign molecules that induces what is called postprandial or metabolic endotoxemia, another term that would have been considered but 10 years ago to be an artifactual term to good understanding of gastrointestinal function. It was not thought that there could be such a thing as a chronic inflammatory burden from metabolic endotoxemia—that you were either suffering from systemic toxemia, which was a critical septic condition in emergency room medicine, or you had normal gut function. But now we see that there is a graded effect and you can, in fact, observe this so-called metabolic chronic endotoxemia that's associated with high fat/high sugar meals (so-called postprandial or post-eating metabolic endotoxemia). And Dr. Cani and Dr. Delzenne have certainly been in that smallest group of investigators around the world that are really pioneering discoveries in this area and helping us to understand how important it is and the consequences of the sequelae associated with inflammatory systemic diseases, but also what we can do about it by modulating and modifying the gut microbiome, the mucus layer of the biofilm of the gut, and also the gut mucosal integrity.

So with that said, why don't we move into our discussion with Dr. Cani and let him enlighten us as it relates to this extraordinary emergence of understanding of the role that lipopolysaccharides from Gram-negative bacterial cell walls in the gut have on our immune system and endotoxemia

INTERVIEW TRANSCRIPT

Researcher of the Month

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http://www.uclouvain.be/en-269734.html

Well here we are, and what a fortune we have with Professor Patrice Cani, who many of you might favorably remember from our visit with him a few years ago from his Metabolism and Nutrition laboratory at the Catholic University of Louvain in Belgium. He and his colleague, Nathalie Delzenne, who have taken over the laboratories of Marcel Roberfroid, have just really advanced this field in ways that are truly remarkable. As I look at Professor Cani's publication record over the last few years, it would rival any top investigator in the world: over 130 publications in top peer-reviewed journals. But more than that is the substance of each of these publications—the breadth, the scope, the depth, and the impact of these discoveries that he and Dr. Delzenne are making are really world changing, and I think that they will have such an impact—a seismic effect on medicine—that we will look back to think of this as a golden age. I think that Professor Cani must take great pride in watching how the ripple effects of his discoveries are influencing so many other investigators.

Patrice, it's wonderful to have you once again as a researcher on Functional Medicine Update. On behalf of all of my colleagues I want to greatly acknowledge and tell you our appreciation for the work that you are doing. It's tremendous.

PC: Thank you so much. That's very kind.

JB: Let's start with postprandial endotoxemia or endotoxicity. This is a topic that not too many years ago would have not been considered respectable to talk about in a mixed scientific audience; there was believed to be no such thing as chronic postprandial endotoxemia. But certainly your work has greatly changed that landscape and understanding. Tell us a little bit about how you got into this discovery and what are the fundamental features that have allowed it to suddenly be recognized as a real phenomenon?

Postprandial Metabolic Endotoxemia: Now Recognized as a Real Phenomenon
PC: That is an interesting point. As you mentioned, this metabolic endotoxemia—this increase in plasma lipopolysaccharides (LPS)—it took a long time to demonstrate to the scientific community…not to demonstrate, to accept that this phenomenon exists. And we came to this theory because we had in mind that obesity and type 2 diabetes are associated with a low-grade inflammatory tone. We are still seeking the triggering factor, but at that time (10 years ago) we were investigating the role of gut microbes following prebiotic treatment, and we knew that prebiotics were able to change the gut microbiota composition and were able to improve the phenotype of obesity and diabetes and reduce low-grade inflammatory tone.[4] And we had in mind that some signals coming from the gut's microbes might be, in fact, involved in this crosstalk between the intestine and the different organs, thereby leading to the development of low-grade inflammation. So we investigated whether some specific compounds from bacteria might be found in the circulating blood, and we knew, of course, from the previous work and old work that our cells are able to express receptors (specific toll-like receptors), for instance, that are able to sense different signals from the microbes.[5] And we decided to measure LPS in the portal veins of mice fed with a high fat diet, or mice that were obese and had type 2 diabetes due to a genetic mutation. In fact, we found that in both models—I mean nutrition-induced obesity or genetically induced obesity—the plasma LPS levels were increased.[6] But this increase was around two- to three-fold the basal level. So we are not in the context of an endotoxic shock. It's completely different, but it was really consistent. In all the different experiments that we performed we found this increase in plasma LPS. We decided to verify whether this increase in plasma LPS might be the triggering factor involved in insulin resistance and in

the level of inflammation associated with obesity. By using different models—we'll not enter into details, of course—but we used models of gut microbiota modulation, we used models of mice that were created for specific receptors of these LPS or core receptors (toll-like receptor 4 or CD14 knockout mice), and we found that these mice lacking the receptors for this LPS were resistant to diet-induced obesity, and low-grade inflammation also.[7] And then we investigated in humans whether we could find a relationship between high fat diet feeding, obesity, and plasma LPS, and we do find this positive relationship between plasma LPS levels and obesity, or plasma LPS and fat feeding. In normal chow-fed mice or in humans we could demonstrate that eating fats is associated with an increase in plasma LPS, so in physiological conditions, fat feeding increases plasma LPS.[8] But we do believe that during obesity and chronic high fat feeding, there is a permanent and persistent increase in plasma LPS, leading to this low-grade inflammatory tone.

This is exactly what I am still believing, but we investigated the gut barrier function, because we know that we are living with a tremendous amount of microbes within the gut, and almost no bacteria are in the circulating blood, so this gut barrier must be really efficient. And we found, indeed, that in obese and type 2 diabetic mice, there is increased gut permeability, so not good gut barrier function.[9]
We decided in the following years to investigate this gut barrier function at different levels, because we know that the gut barrier is composed, of course, of epithelial cells, the tight junctions are really important, the antimicrobial peptides produced by the epithelial cells are also important, but we also know there is a mucus layer, and this mucus layer can also contribute to this gut barrier function. And so we found by using different models that all these different barriers might be altered during obesity and type 2 diabetes. For instance, we found increased gut permeability by mechanisms linking tight junction distribution; I mean, localization and expression. We found also a reduced mucus layer thickness, for instance, in diet-induced obese mice.[10],[11]

We found that high fat diet feeding reduces the expression of anti-microbial peptides, so this crosstalk between microbes, the host, epithelial cells, and finally metabolism exists, but we are still now trying to understand exactly all these complex pieces of the puzzle. But anyway, what I think is that there are some signals coming from the gut microbiota that will lead to the development of inflammation through changes in this gut barrier function.

Developing LPS-Measuring Technology
JB: What you just said obviously validates my introduction: life-changing, world-changing, paradigm-changing concepts. Let me, if I can, ask a little sidebar question. Often we see these major discoveries occurring on the shoulders of certain kinds of technologies that were not available before. In other words, we can ask certain questions to find answers for those questions that we couldn't find answers for in the past. I think your ability to measure accurately LPS at very low levels at high sensitivity was a major advance because it appears to me that before people might have speculated, but they didn't actually have the technology available to measure LPS at low levels. How was it that you were able to define an LPS-measuring technology that would give you the kind of sensitivity and precision you needed at these low levels?

PC: That's a good question. I have to mention that measuring LPS is still a nightmare. I mean, you have to be careful because when we are measuring LPS, we have to perform very good blood sampling. We know that, for instance, LPS can bind to plastics. We know that LPS, or endotoxins, are everywhere, so we can contaminate samples or we can also find false-negatives. We are still using the gold standard

method, which is based on the limulus amoebocyte lysate (LAL) assay, but we are now in the conditions where we know that we have to introduce in each of the samples a known amount of LPS to calculate a recovery. So what we do now when we measure LPS is to measure and duplicate each sample, but we have to also duplicate a recovery. So we spike the samples with a known amount of LPS, and when we are measuring LPS, if the recovery is below 100 percent—let's say, for instance, 20 percent—it means that we are in a condition where the samples are inhibitory. It means that we cannot trust in the data. And that's the reason why sometimes, and most of the time, people said, we couldn't find LPS in normal conditions because there were inhibitory conditions, I guess. So they didn't try to verify if indeed the plasma was inhibitory for the reaction. And it means that now that we know that LPS measurement is really a tricky method, we have to be careful about not only the contamination, but also about the specific inhibitory reaction.

I can give you a very simple example. We have a sample where, when we measure the plasma LPS by using these methods without recovery, for instance, the method will say, "None detectable." So you have no LPS. But if you perform exactly the same measurements with the same sample but you put a known amount of LPS, you know that you have LPS in your sample. But the method will say there is zero LPS in your sample. And the recovery means that you have zero recovery—you couldn't find, you couldn't measure, the LPS you put in your sample. So I think that now knowing that we have to move toward this kind of measurement to really trust in our data, to be sure that in each of the samples that we are assessing we have a known amount of LPS and a good recovery, that for me is the key point. This has not been performed previously in most of the studies. So, in other words, I think that now we have data in hand to measure in a very accurate manner and a very low and high sensitivity manner the plasma LPS by using LAL methods, and I'm using for instance, kinetic color measurements, and we can measure through 0.005 ug per mL, so it's a really low, low level. But this recovery point is a really important point, because otherwise we can say there is nothing, and it's a false-negative, in fact.

JB: Thank you. That's very, very helpful. For the sake of our listeners, would you just give us a quick thumbnail of the nature of lipopolysaccharides? We know they come from the Gram-negative bacterial cell wall. But I don't think for most people they understand, what is LPS? Is it a class of molecules, is it a specific molecule, are there different variations on a theme? Could you just quickly give us a thought about what LPS is?

Lipopolysaccharides Explained

PC: Yes. So, LPS is, in fact, a complex molecule composed of different lipids, so it is quite a big molecule. I will not really enter into all the details, but the components of LPS are different. You have a chain. You have what we can call a core, and the Lipid A. All these different parts of the lipopolysaccharides are in fact specific to the different bacteria. I mean, for instance, we know that the lipopolysaccharides coming from E. coli, this serotype will be different from another one. You'll see also conferred to this LPS this capability to induce, for instance, inflammation. I mean, with one molecule of LPS, from one E. coli and from one salmonella, for instance, we know that the antigenicity or the capacity to induce inflammation will be different.

We are speaking about LPS measurements, but we have to keep in mind that it's a lipopolysaccharide or an endotoxin activity, so it's a capacity of the LPS to induce the inflammatory tone, because we know that some LPS will have poor impact on the inflammatory tone. So this complex molecule—this macromolecule—has a different composition at the level of different lipids, but also carbohydrates. And so

far, nobody can really discriminate in the blood sample the different types of lipopolysaccharides, so we are still measuring the endotoxin activity.

JB: Got it. Thank you, that's very, very helpful. When you then look at, say, different species of bacteria, different strains within the gut microbiome—say the Firmicutes versus the Bacteroidetes—your bacterial cell wall fragments—your LPS fragments—between those two families can have very different inflammatory tone I would presume from what you've said.

PC: Yes, sure.

JB: So as you speciate the microbiome, what have you started to learn about those bacteria that have the greatest potential for inducing proinflammation?

PC: So honestly maybe seven or eight years ago I had in mind that the more Gram-negative bacteria we have in the gut microbiota, the more important the inflammatory tone will be. And then I had to change my mind because of some recent discoveries from the lab. And, indeed, we are still trying to understand what kind of gut microbiota we induce along with inflammatory tone. But we know from our data, including deduced from other researchers, that the gut barrier function is really important. It's what I mentioned before. I think that although the Bacteroidetes/Firmicutes ratio is something important, we cannot say if we have an increase in Bacteroidetes (I mean, mostly Gram-negative bacteria) that will induce a low-grade inflammatory tone, because between the gut microbiota and the host there is the epithelial cells and the gut barrier.

Akkermansia muciniphila: Revealing Research on Prebiotics

I can give you an example regarding one specific strain we have identified and characterized. This is Akkermansia muciniphila. This bacterium—this Gram-negative bacteria—and we in fact investigated the role of prebiotics (we are now in 2007), and in 2007 I had the chance to measure by using power sequencing, so a high-throughput method, the composition of the gut microbiota in mice that were fed with prebiotics. So we knew from Marcel Roberfroid's work and from Glenn Gibson that of course prebiotics will increase Bifidobacteria, and in some cases Lactobacilli.[12] But we decided to investigate more into this gut microbiota, and we found—this was serendipity—we found that prebiotics were able to increase by about 100-fold, one specific strain: Akkermansia muciniphila (see reference #6). And honestly when I received the data, and I saw that—that it was a Gram-negative bacteria—I said, "My God, it's impossible." Because we have published data and we still have data in hand showing that prebiotics in the context of obesity and type 2 diabetes reduces plasma LPS, and here I have data in hand showing that I have a very huge increase in one Gram-negative bacteria, and this is Akkermansia muciniphila. And finally, by using different methods, and we have published this paper now, we found that this Akkermansia muciniphila was not so bad. It's not really a bad guy. We know that this Akkermansia muciniphila, although it is a Gram-negative bacteria, it's LPS. It's like lipopolysaccharide. It's a very poor LPS to induce inflammation. And we also found that this bacterium improves the gut barrier function, so the more Akkermansia muciniphila we have, the better is the gut barrier function. And we found that in diet-induced obesity Akkermansia was decreased, and there are also some data now in the literature showing that in obese patients or in type 2 diabetes patients, this Gram-negative bacteria is, in fact, decreased (see reference #11). I mean, the abundance is lower, suggesting that this specific Gram-negative bacteria may have a positive impact.

So it might be really difficult now, from my point of view, to say we have to blame all the Gram-negative bacteria. I think that we have to look more precisely at the gut barrier function. Of course, you know that from many, many years, but I think that in the scientific community, most of the scientists that were not really aware about this gut barrier function are now jumping into the story, and this is true for hepatic steatosis, also, and different diseases, where the scientific community is coming back to this previous story of the gut barrier function and nobody was trusting it, and now they are. I think they are interested, at least, in this investigation of the gut barrier function. So I think that this Gram-negative/Gram-positive story is one thing, but we have to put in between the function of this gut barrier.

JB: That was beautifully stated. I certainly would agree with your assessment that the scientific community is moving in this direction. If you just look at the number of publications since you and Dr. Delzenne started publishing in this area, it is exponentially increased, and I think a lot of that is a consequence of the great science that you've done. Let me, if I can, talk about this concept of the receptors for which these bacterial debris have their influence. You talked briefly about toll-like receptor 4. We also know about the endocannabinoid receptors. We know about them as members of the G protein-coupled receptor family. You've done some work and published on GPCR 43.[13] What do you think the receptors are that are being influenced by these metabolites from bacteria. Are there multiple receptors or are there specific families that are more dominant in controlling this inflammatory tone?

PC: Okay, that's a very good question. I think that based on the pharmacological properties, we cannot say there is a unique type of receptor involved in the crosstalk between microbes or metabolites coming from microbes and host. For instance, as you mention, there are some receptors for metabolites that are just short-chain fatty acids, so GPR 41/43. There are some receptors for endocannabinoids—GPR 119, for instance—or others. And we have had some data indeed suggesting that we have to take into account not only the expression of these receptors—where they are localized on the gut or on the different organs or on different cells—but also how the gut microbiota are able to crosstalk with the host through these kinds of receptors. And we, and others, have investigated the role of GPR41 and 43—how they can contribute to the improvement of, for instance, secretion of GLP1 or GLP2, so two key peptides that we have investigated.

But I think the picture is not clear so far. We are at the beginning of the story, I think. This is my point of view. I think that we still have to discover different types of receptors. Whatever the kind of receptor—GPR receptors or ion receptors or whatever the type of receptor—but I think that we are at the beginning of the story. Because it might be possible that we have endogenous receptors that have been described so far for endogenous molecules that are able to respond to some specific metabolites from the gut microbes. So we may not exclude—and this is probably the case for the endocannaboids also—that some microbes are able to produce metabolites that will be considered as a ligand for specific receptors, and finally, will probably contribute to explain the impact of the gut microbiota composition—it's functional activity. I mean, we are still trying to understand not only the gut microbiota composition, but also the metabolic functions encoded by these microbes.

Adipocytes May Respond to Specific Metabolites in the Gut Microbiota

I think also that we do not have to consider only the receptors present on the epithelial cells, but also receptors that are present in innate immune cells or immune cells at the level of the intestine, but also in the adipocytes, for instance. So we have data now that suggests that the adipocytes may respond to specific metabolites coming from the gut microbiota (I mean short-chain fatty acids). So it's really an

expanding science. I would like—and I look forward to seeing—whether some other kind of family of receptors will in fact be specific receptors for metabolites coming from microbes. We are speaking about gut microbes, but we may not exclude that some viruses or components of viruses might also contribute to this phenomenon. I mean, we have in mind, for instance, MyD88, which is a component of the toll-like receptors.

JB: What you've said is extraordinarily important because you've talked about the crosstalk among macrophages, adipocytes, and these gut receptors that are activated by bacterial metabolites. This is a whole new systems biology approach towards health care. I want to shift just quickly to the diet influence, because you've published some very interesting papers in which you talk about things like curcumin and its influence on these inflammatory processes of the gut, and a paper you did on tetrahydro-iso-alpha acids derived from hops and its influence on endotoxemia.[14] The question that one might ask is, are these phytochemicals coming from various foods and spices directly acting as antagonists of the endotoxemia, or are they indirectly working by modifying the gut environment, changing the bacterial speciation? In other words, are they influencing the receptors of the endotoxins or are they actually changing the bacterial flora so that there are different endotoxins being produced? Do you have a thought about that?

PC: That's also a very good question. I think that I have no clear answer. I mean, all these different mechanisms might be involved. For instance, we know that some phytochemicals are able to change the gut's microbiota composition. Is it directly through the targeting of specific microbes, or is it through mechanisms changing, for instance, the pH or the environment within the gut? It's possible. Is it through the modification of antimicrobial peptide secretion from the host? I mean, it's also possible. So I think that so far I have no clear explanation. What I can say is that the different components we have tested are able to improve the gut barrier function. They are able to reduce plasma LPS levels, and to improve the phenotype (I mean, to reduce inflammatory tone), and this is associated with the change in the gut microbiota composition. But honestly, we are still investigating these kinds of questions: if it is directly through the modulation of the gut microbes, or through any modification of this crosstalk existing between host-microbes/microbes-host? But anyway, I think it is important just to keep in mind that they are efficient, so some specific phytochemicals are really efficient to improve the phenotype. Then, what kind of mechanism it is, it is also an important point maybe to design specific drugs, but we have so far enhanced natural compounds that might be useful. We spoke about the prebiotics, of course, but there are so many different compounds, and we have worked—and you know that, of course—with different alpha acids that were really efficient to reduce this, for instance, inflammation, to reduce body weight gain, to improve gut barrier function. And I'm still looking for what are key mechanisms: who is doing what and how it works.

How Does Gastric Bypass Surgery Influence Obesity and Diabetes?

JB: Thank you. So, let me shift maybe to the last question. I would love to engage in this discussion for hours but I know time is limited, so let's talk a little bit about the extraordinary discoveries you've made as it relates—as you've alluded to—to the role of these inflammatory processes, both in obesity and in diabetes type 2/insulin resistance and the manifold effects that occur as a consequence of insulin resistance. When I look at that series of publications that you've had from your group, which I think are extraordinary in helping us to understand that the gut and its speciation within the microbiome has something to do with obesity and with inflammatory disorders associated with diabetes, it then raises a question as it relates to medical practice today, in which we're seeing a lot of gastric bypass surgery like

Roux-en-Y being done for people with morbid obesity: how does gastric bypass actually influence obesity and influence diabetes? It's not just strictly a calorie control/malabsorption syndrome. I know you've published at least one paper in this area.[15] What is your thinking right now as it relates to the influence of gastric bypass on these complex mechanisms of the microbiome and inflammatory signaling?

PC: Yes. Honestly, I'm pretty convinced that there is a link with gut microbes. There are data, and really ligand studies that have been published now. I have in mind one key study published by Lee Kaplan's group in Science Translational Medicine magazine last year. And they have found that gut microbiota coming from mice that were in fact treated—I mean, they had surgery, this kind of RYGB surgery. So what they did is to treat mice by this surgery, and they found that the mice fed with a high fat diet of course were losing weight, and the gut microbiota was completely different between the RYGB and the sham operated mice. When they transferred the gut microbiota from the RYGB-treated mice into naïve germ-free mice, and then they fed the mice with the high fat diet, they were as resistant to diet-induced obesity. So it means that by simply transferring the gut microbiota harvested from these RYGB donors into naïve germ-free recipient mice, they could replicate the phenotype of the surgery itself, meaning that indeed there is something really crucial, but what, exactly, we don't know—but something coming from the gut microbiota leading to this protection. And in this context—and in this study—they also found a very strong link with Akkermansia muciniphila, so this bacterium that I discussed before that we discovered, they found that following this surgery, Akkermansia muciniphila abundance increased really highly—toward 20 percent of the gut microbiota was represented by this bacteria. And it has also been demonstrated in humans that RYGB treatment increases this bacteria.[16]
Now the question is: is it through this bacteria, or through an interaction with other bacteria? I don't know, but we have evidence showing that indeed RYGB treatment changes gut microbiota composition, and we can replicate the phenotype by simply transferring the gut microbiota into naïve germ-free mice. So my answer is yes, we have to look more specifically, at this level of the gut microbiota. What kind of metabolites are produced? Is it through a specific activity, a complex of microbes, can we, for instance, design three-, four-, five different bacteria and put together these bacteria to replicate the phenotype? It might be possible. But the RYGB treatments, yes indeed, contribute to the decrease in body weight I guess through a gut microbiota-determined mechanism. Now we have to prove that in humans, of course. It's clearly and nicely demonstrated in mice.

JB: And do you feel that there is, at least early stage evidence from fecal transplants that are being done in humans, some positive directional indication that this model will prove useful therapeutically?

PC: So far, the transfer that has been published—I mean, in humans—they have shown an improvement of insulin sensitivity without any change in fat mass or inflammation and body weight.[17] I think that it is still too early to say that will be the next treatment for obesity, but I think that also if we can improve the phenotype of an obese subject—I mean, if we can reduce insulin resistance, reduce low-grade inflammatory tone, and improve the mobility, that's the first step. Then, if we are able to reduce fat mass, it's the second step. But in a clinical point of view, I think that one day we will be able to design, maybe, a specific mix of bacteria, or we will maybe find a super donor—we don't know—that will help to improve the phenotype. But we have to keep in mind that when we are transferring (I mean in humans) microbes (gut microbiota, or fecal transplant), it is also associated with a transfer of different viruses and different other components. So it's complex. I mean, we are at the beginning of the story of obesity, not in the context of Clostridium difficile resistance. I mean, really in the context of obesity. So my point of view is

yes, I think it’s a good model to understand the relationship between microbes and host. If it’s the next treatment, I’m not yet convinced.

JB: I want to thank you, Dr. Cani. Your work and that of your colleague, Dr. Delzenne, is just truly paradigm-shifting. It’s so exciting to check in with you and see the progress you’ve made just in the last few years, since our previous discussion on Functional Medicine Update. We wish you, obviously, continued great success. This is, to me, changing the way that people actually view not just specific therapies, but the whole nature of medicine, because what you are doing is tying together gastroenterology with immunology, with rheumatology, with cardiology, with neurology. I mean, it’s really breaking down the barriers among different medical disciplines and creating a whole system of biology that will create an effect on reduction of incidence of, I think, preventable and treatable chronic disease. Thank you so much from all of our listeners. We wish you the very best and hope to keep in touch with you and follow your publications very closely.

PC: Thank you very much. Bye-bye.

JB: Bye-bye.

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