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Welcome to *Functional Medicine Update* for January 2014. You know, each year, when I introduce a new year, it seems quite remarkable to me, given that we've now been doing this going on 32 years. It just strikes me as both amazing how quickly time goes by, but also the breadth and depth of material that has gone over these 30-plus years as it relates to the evolution of medicine. I was reminded of this when I read, just this last week, a very interesting report from the University of Washington School of Medicine. Two geneticists have just determined that there is a code that lies underneath the genetic code that we all learned from the Watson and Crick days in the early 1960s, things that I committed to memory for tests that I took in the early sixties when I went to college. And now we find out that there is another code that lay dormant, quiet, stealthily below the code that we all had learned, that actually informs how the other code is going to be read, meaning it's a code within a code.[1]

Think of the implication of what this means for just the advancing understanding of genetics. We think we know so much, and we do know a lot, but yet there is so much we don't know. This, of course, is what separates the sophomoric wise fool from the individual who is always seeking the frontier of new knowledge, knowing that what they knew yesterday may be replaced by something they learn tomorrow that actually revolutionizes thinking. That's exactly what we are going to be confronted with, here, in the first two issues of the 2014 year of *Functional Medicine Update*. You are going to be privileged, as I was privileged, to be informed by two world leaders in the area of gastrointestinal health, from a perspective that I would call remarkable, game-changing, ground-breaking, paradigm-shifting, and revolutionary.

It's almost, however, back to the future, because it takes us back to some of the early reports of people like Ilya Mechnikov, who at the turn of the last century was speaking about prolongation of life by the installation of *Lacto bulgaricus* forms of bacteria into the rectum for reinstilling proper bacterial flora into the gut for health—the prolongation or life—or consuming orally various forms of yogurt or kefir that were cultured products that had these live bacteria for improvement of health. And of course this was ridiculed for so many decades as being facetious, silly, nonsensical, nonscientific, artifactual, and all sorts of words, some less complimentary than others, that would marginalize this concept, saying that it was a thought without proof. But as you will learn through the lens of two extraordinary investigators, Dr. Alessio Fasano at Harvard Medical School, and Dr. Gasbarrini, arguably one of the top gastroenterologists in Italy, who will be our February *Functional Medicine Update* clinician/researcher of the month, you're going to learn that what was old is new—that we have actually been able to start understanding this complex interrelationship between our diet, our living microbes in our gut (the so-

called microbiome), and our systemic health, to the point that it's leading to a whole revolution in thinking about the origin of chronic illness and both how to prevent and manage it, and also to understand the epidemiological epidemic that we're seeing—almost a pandemic, globally, of the rising tide of chronic illness as we start seeing changes in diet, changes in environmental pollution, changes in stress patterns, and how that translates into just a virtual pandemic of incidence of diseases that used to be relegated to a small fraction of the population at the terminal end of their life, and now we're seeing it start to penetrate down into younger years with greater prevalence, things like type 2 diabetes, neurologic nephropathic ocular injury, dementia, cardiovascular disease, dyslipidemias, inflammatory conditions, arthritis, autoimmune disease, digestive disorders of nonspecific origin. All of these which we see as changing patterns of health are interrelated to this extraordinary paradigm shifting revolution in understanding that we are being confronted with, that you'll learn more about from our clinicians of the month—our researchers of the month—in these, what I would call, epic January and February issues, 2014, of *Functional Medicine Update*.

Jump on the train. We're just about ready to leave the station, and you're going to be having a really interesting journey with us over the next two months. With that, let's turn our attention to one of the world's foremost experts in what we consider gluten-related dysfunctions, Dr. Alessio Fasano, and get some direction from him as it relates to this transition/transformation that's occurring in thinking, and then we'll come back and regroup and have some thoughts after his discussion.

INTERVIEW TRANSCRIPT

Clinician/Researcher of the Month

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We are fortunate to have as our clinician/researcher of the month an individual who is arguably, I believe, probably the top—or one of the top-rated—presenters that we have ever seen at the Institute for Functional Medicine International Symposia over the last 23 years. For those of you that were at the meeting, you know who I'm speaking to and that is Dr. Alessio Fasano, whose name and reputation really precedes him. It's remarkable to see what Dr. Fasano has done in terms of opening up this field of understanding of this complexity between food and the immune system through the interaction of certain reactive proteins in food that are members of the family that we call gluten, but then really beyond that to this whole threshold issue of how information and food can be picked up by the immune system of the body and translated on an individual basis based on genetic uniqueness into information that would be considered alarm information that we often call disorders of inflammation or autoimmunity. I think we have had a lot of history of working around this topic, but we have never had the privilege until the last 10 or 15 years of having someone with the insight, precision, and doing the heavy lifting in science of a Dr. Fasano to really add substance to the understanding of this topic.

Alessio, it's wonderful to have you here. You are, I know, extraordinarily busy in your position as the Director of the Center for Celiac Research at Mass General Hospital, and being a visiting professor at Harvard Medical School in Pediatrics, and publishing widely, engaged in research and grant writing, and really, I would have to say, being a central figure in changing the context of medicine to really look seriously at how nutrition, diet, and reactive substances in food influence health. Thank you for being part of our Functional Medicine Update.

AF: Thank you, Jeff, for having me. They are very flattering words.

JB: Well, certainly well-deserved. For those listeners that were not fortunate enough to hear you speak, which—by the way—was one of the most eloquent presentations I've had the fortune of hearing, where you talked about the research method, and the development of a hypothesis, and what led you down the trail into this extraordinary detective story surrounding gluten and celiac disease. Maybe, for our listeners that were not so fortunate to be there, you could kind of give a brief overview as to how you traveled through your intellectual journey from Italy, to North Carolina, to Maryland and to the Mucosal Disease Research Center, and ultimately, now, to Mass General—how your intellectual process evolved.

Studying Pathogens: The Interplay Between Host and Environment

AF: Sure. I mean, it's a story of serendipity, as usual. When I was a medical student I was very much interested in diarrheal diseases, while I was in training I joined a lab that was a strong lab in terms of diarrheal diseases and gut physiology. I studied, for several years, how the intestine really reacts when attacked by microorganisms that cause diarrhea. Then I reached the point at which I felt that I knew one side of the coin and I needed to know a little bit more of the other side—what bacteria do in order to cause cross-talk with the host. My mentor suggested I spend a couple of months in the United States to learn a little bit about bacteria pathogenesis, and particularly cholera; that was the pathogen that I was very much interested in because it was still causing tremendous amounts of morbidity and mortality in the population. He sent me to Baltimore, to the Center for Vaccine Development, to spend a couple of months there. And this couple of months became two years because I was in the right place at the right time with the right people, and several discoveries were made. That became quite an exciting time of my professional career. You know, after these two years I had to go back to finish up my fellowship and to wrap up what I was doing in Italy. This was in the late 80s. By October 1992, I got a phone call from the department chair (pediatrics) in Maryland who said, "We want you to come back and for good, to be our division chief." Talk about a total shift of lifestyle. My English was still broken English, and I didn't know anything about the rules of medical practice in the United States. I didn't even have a visa. But, bottom line, I decided to jump on this opportunity at a relatively young age; I was in my mid-30s. In 1993 I moved for good, and from there I started this journey from the diarrheal diseases, to trying to understand how pathogens cross-talk with us and trying to understand what are the mechanisms they engage? Interestingly enough—not because by design but because science brought me from one point to another—this kind of discourse led to better understanding of the interplay between the host and the environment that leads to autoimmunity. Celiac disease was already a clinical interest of mine, and it became a unique model to study this interplay in terms of autoimmunity, and the rest is history.

JB: I think that "the rest is history" is so fascinating to watch the evolution of your publications. I've had the privilege—I can't say I've read all of the more than 200 of your publications, but I have read, I think, a critical number of them to kind of get the ebb and flow of the texture of your work. You can actually, I think, by following your publications, almost do a history of the evolution of gut immunology and this

complex interaction between the microbiome, the gut enteric immune system, and the diet. I think through your own work we're actually seeing the evolution of a historical paradigm shift in medicine. Have you had support from your colleagues in the broader gastroenterological field for this—what is a remarkable, I think, kind of perspective of change and thinking about the GI system and its relationship to the gut bacteria and the diet?

Transformational Science Leads to Discoveries About Celiac Disease and Autoimmunity
AF: Well, Jeff, there are two kinds of science I believe. There is the incremental science, so you go from Point A to Point B, from Point B to Point C, and so on and so forth. So you know where you are starting and you know where you are leading to. This is a science, and in general it is supported by peers because they see it. They understand what you are trying to do, and in general you do this incremental science by relying on what has been out there in terms of the literature, so it's their own work that is cited, that is the basis of what you are doing this on. That is the accepted kind of path. And then there is transformational science. The one that is really a total shift of paradigms, think out of box, the stuff that is high risk because of the time you are wrong, but if you are right, really you change, completely, the landscape and open different kinds of avenues. By definition, this is not that popular, because you go against wisdom, you go against the establishment. It's a little bit more complicated and hard to be accepted.

Not because of design—I didn't decide that way—but most of my scientific career has been transformational science, because I stumbled upon it, and therefore I really had a hard time. I can list many times in which, for example, starting with celiac disease, when we started to claim it was not as rare as was believed to be in the United States, but was overlooked, I can't tell you how many times people criticized that point of view to the point in which some of my close friends and colleagues said, "What are you doing to yourself? You are ruining your accreditation and therefore your career. Why do you do this to yourself?" Again, it turns out to be that, indeed, that was the story, and now nobody will even dispute that celiac disease exists in the United States. Same story in terms of autoimmunity. For example, the general wisdom that still holds true to many classical immunologists is that autoimmunity is a one-way street. Once you get in there, you can't come back because it is totally irreversible. There is nothing you can do about it because it is the result of antigen mimicry, or by standard effects, so you lose the capability, and there is no way that you can rewind the tape. Celiac disease is just otherwise. If you can really block this interplay between the host and environment—and in celiac disease we know the environmental trigger, so you can really do that—you can stop autoimmunity. This was a complete shift of paradigm that was really not well accepted and now I believe most people would not dispute that. When we had trouble with the most complicated part of the story…when we put into the picture of the recipe of autoimmunity—a third ingredient besides the genetic disposition and environmental trigger—namely, the loss of intestinal barrier function so that intestines can't keep out the "enemies," the cell antigens that will instigate the immune system to lead to autoimmunity, that was another major shift in paradigm that created all sorts of criticisms because, of course, many colleagues say, "Now you are embracing the leaky gut theory that is bogus, it's not true, and so on and so forth."

Again, in all these examples, you can just express your opinion based on your honest, humble observation, because what a scientist does is not invent anything, or to score anything; you just listen to nature, because the stuff is already written. Either you are a good listener or not. If you are a good listener and therefore rather than to try to force on nature your concept, you are just are there to serve what is already out there. The chance exists all the time, even at the beginning you will have a really hard time, the facts will speak for you and not "my opinion versus yours." Again, in all of these examples I gave

you, when we proposed that kind of shift of paradigm we were not well accepted, then the evidence in the literature and the accumulation of data became so overwhelmingly clear that I think that nobody will dispute again that autoimmunity requires three elements including the intestinal barrier dysfunction—that the autoimmune process is not a one-way process anymore, but if you can find a way to stop this interplay between environment and host you can do that. You can really bring back these people. There is definitely an element that is crucial—that is, change the environment—to explain these epidemics in plus-50 years of autoimmune diseases. Nutrition is probably the key element that changes everything and these impinge on the composition of the microbiome that seems really to be the yin and yang between tolerance and immune response in people that are genetically disposed. All these concepts that we are at the forefront of out-of-the-box thinking, I believe are now coming into the mainstream pipeline of thoughts and we're glad.

JB: Let me take a deep emotional and intellectual breath with the listener, here. I think every senescent human being that just listened to what you said over this last few minutes, which was so eloquent and so word efficient in projecting many, many thoughts about the evolution of ideas, the change of culture, discovery, innovation, reduction of human suffering—that was all incorporated so eloquently in your previous thoughts. I hope every one of us listening are taking this in, because it's a model for how humans progress in time and culture, and overcome barriers of static thinking, and produce a dynamic change in society. I'm reminded that this hinges on the scholarship of your work, because in the end, the more revolutionary the discoveries the more it requires the diligence of the heavy lifting of proof of concept, which you've done very, very nicely through exquisite science. Your discovery of Zonulin, and the interrelationship of these interesting proteins that are messenger molecules that interrelate gastrointestinal environment to systemic responses and things like how calprotectin interrelates with the barrier function of the gut and how that connects to Zonulin. These are all new concepts that have come out of your laboratory. Was it a consequence of you bringing into your laboratory individuals with diverse talents that help to make discoveries out of the area of the common path, or did you, yourself, kind of travel into these uncharted waters to find out how to explore these processes?

AF: Oh Jeff, this kind of science required a team and not a single individual. The single individual can come up with intuition, but it takes a village, so by all means whatever we accomplish is a consequence of a team of dedicated individuals that share the kind of vision. I personally believe that if you want to do good science, you have to have very clear in mind what is the ultimate goal. In my experience, if the ultimate goal is career success, fame, you're going to fail, because you are blind to what is really the ultimate goal. If the ultimate goal is to improve quality of life for people and try to understand why people eventually move from a state of health to a state of disease, then the fame, the discoveries, that will become as part of a collateral—not a primary—goal. Now the key element is to choose the team that sees the same way as you see, and that's the only thing that I did. In other words, I may not have had in my lab, as collaborators, maybe ten Nobel Prizes, but definitely I had the people that were raising the same concept of what is our ultimate goal? Not seeking fame, or money, or God knows what—promotion and grants—but make sure that we never got distracted from what is our final destination. This brings also some interesting facts about dichotomies that I still don't understand. For example, traditional medicine versus complementary medicine, functional medicine versus evidence-based medicine. I just don't get it. And again, these are polarized points of view that I believe are making a disservice to what is indeed our final mission, here. Because I'm pretty sure that a functional medicine doctor and a classically trained traditional doctor have the same kind of final goal. It is the methodology that changes, maybe, but not, definitely, the goal. I don't understand why one has to be right and, by default, the other one has to be

wrong. If you look at just the history of medicine and discourse, Chinese medicine, clinical medicine, Arabic medicine, the Greek and Romans, they were healers, so they were taking care of the single individual. Over time we decided we had to make rules, because otherwise you cannot really come up with some intellectual explanation for what are the phenomena we look at, and therefore we move to the large numbers, the epidemiological studies, the evidence base, the algorithms, i.e. the way that we now function. We made these kinds of rules because we assumed that there is homogeneity in that disease. When you talk about celiac disease, we talk about the same thing, and therefore the assumption is that the approach has to be the same, the solution has to be the same, no matter who you are. Now we realize that we were wrong. Indeed, now we move to the next phase in which everybody will agree that personalized medicine, physician certification for customized approach is the way to go. So what is the difference between these two worlds? I don't see it. It's just a matter of methodology.

JB: Very well said. I want to give you a gift, just quickly. I know you get these gifts all the time, which are feedback from patients who have benefitted from these ah-ha moments that you have helped provide to them. We have two leaders—clinical leaders—interviewed on Functional Medicine Update years ago about their own personal experiences (what I would call the classic "ah-ha" personal experience) with their own health issues that tied back to discoveries that they made in themselves thanks to you. These two individuals both spoke about the fact that they had developed progressively more serious neurological issues, one leading to multiple miscarriages and very serious musculoskeletal disability. They were in an academic setting as a faculty member, seeing the best of their colleagues, not finding remediation, and they happened to come on to your work. They went on to a gluten-restricted diet and within about a year they had completely recovered their health. This woman went on to successfully have a child after these multiple miscarriages, who now, by the way (it's enough years) that child has turned out to be a star student who is going to go on to medical school, and credits her life in finding your work. In that same issue of Functional Medicine Update, another clinician—a doctor in private practice, in this case—was a woman who started to develop nonspecific kind of encephalomyelitis. It looked like she was becoming demented. She was losing her memory, losing her language skills, thought it was MS but it really wasn't MS. She just couldn't come to a clean diagnosis. She was unable to drive her car, had to give up her practice, and then, again, found your work through someone who suggested that maybe this work of Dr. Fasano might apply to her situation. She went on a gluten-free diet and again talks about her story in this interview, which has completely transformed her life—put her back on the path to good health and has transformed her practice now in New Hampshire, where her focus is dealing with this problem with patients. This translational concept, from the lab to the bench, from the bench to the bedside, to the clinic, to the individual, this is something that very few people in research ever get a chance to see. It must give you a great sense of joy to actually see these discoveries you're making actually make such a meaningful difference in people's lives.

Perseverance: The Best Trait of a Good Scientist

AF: Oh Jeff, first of all I sincerely appreciate that you shared these stories because we live for this kind of stuff. The purpose of science without applicability really doesn't satisfy or give you the sense of accomplishment. But when your science really makes a difference in the lives of individuals, even a single one, that is worth any kind of price that you can imagine, because that's really the kind of legacy that I personally believe will make sense and justify the tremendous amount of work and sacrifice that you do in embracing this kind of profession. We talk about the results that you publish and the success, but for each one you probably did hundreds and hundreds of experiments that didn't go well. I keep telling my students and fellows, I say, "The best trait that indicates a good scientist is perseverance

because you need to delay rewards." It doesn't come right away. But when you have stories like the ones you just shared with me, these are priceless. I can't really put the right value to what this means. Again, studying a molecule like gluten that is a protein from a grain—supposedly it is supposed to be a friend—and try to make sense of why this friend has become a foe, it has been quite an extraordinary journey for us. And again, it is a shift in paradigm when we start really to find out that this is creating a problem not just for people with celiac disease, but everybody, we get hammered by our colleagues with, "What are you talking about? The only way that you can get in trouble with gluten is celiac disease, and if you don't have celiac disease there is no reason to even consider gluten-free diets or to do anything about it." And then over the years we realized something that I found extremely fascinating: that gluten is treated by our immune system as a component of the microorganisms, so it induces the same response that we would have if we had been exposed to bacteria. As such, we see this response that is common to everybody. This must be the consequence that gluten was a mistake of evolution—that we're not supposed to eat this gluten because it came into the picture only in the last second of the 2.5 million years of humankind evolution, with the advance of agriculture ten thousand years ago. Again, I believe that like bacteria, even if everybody, when exposed to them, they have an immune reaction, but not everybody develops an infection. So not everybody who eats gluten will get sick because of ingesting it. The vast majority, as a matter of fact, will eventually fight this enemy through the immune system, and will not even know this fight is occurring. There are a few that will lose the battle that will eventually develop problems like the outcome that is celiac disease, or the allergic reaction like with allergy or like these two examples you just gave that may not be celiac but gluten sensitivity.

JB: You just authored a fascinating paper that is co-authored with many of your colleagues, which I find just philosophically interesting. It's titled "Non-celiac Gluten Sensitivity: The New Frontier of Gluten-Related Disorders" and appeared in the journal Nutrients in 2013, volume 5, page 3839.[2] It's a very powerful review, but it's also very interesting philosophically because the co-authors on this paper represent leaders in their field across many countries—Italy, France, Spain, Germany, Buenos Aires in Argentina, United States (Columbia University). This is a tour de force. Tell us a little bit about how this article actually was put together with these multiple authors.

Non-Celiac Gluten Sensitivity: A Multi-Disciplinary Group Comes Together for Discussion
AF: Again, because there are very few facts and a lot of fantasies, we decided that the best way to make the point of what is the current situation of non-celiac gluten sensitivity was to really put around the table the who's who about celiac disease and gluten-related disorders. Jeff, needless to say this was a very interesting exercise because there were believers and non-believers, traditional thinkers and progressive thinkers. These two days of brainstorming around the table with these 30-plus people, coming to meet from every corner of the world, was an open mind experience for me that I was motivating the discussion. Again, you can see how, during these two days, you started with preconceptions and walls of consideration about the topic, and while discussing this, these walls came down and people started to really open up to constructive possibilities to try to understand what are the facts and what are the fantasies. The result is that is the review that you just mentioned that indeed is a scientific review but also a philosophical testament, if you wish, of what is a critical thinking of an open mind approach to a topic that is fascinating to say the least. I don't think that anybody, even the most skeptical, will doubt the existence of this new entity. And again, this was something that we put forward three or four years ago with a couple of papers that proved that this was different from celiac disease. This news was not accepted that well by the establishment, but now even some of them reluctantly admit it exists. Now, what exactly this is all about is still an object of discussion, and that's where I believe the line of research

will materialize over the years. I was skeptical myself, but when you have examples such as those you mentioned of these two colleagues, there is no way that you can support the notion if you don't have celiac disease you don't have any business going on a gluten-free diet. How do you justify this tremendous improvement of symptoms in people they have experienced for so long just going on a gluten-free diet without having that open-mindedness that there is something beyond celiac disease that can bother people when exposed to gluten? That's pretty much what materialized in this consensus conference that led to this publication.

JB: I want to spend the last couple moments, if I can, with you, kind of crossing a very interesting bridge that I know you're crossing or have crossed. I'd like to vicariously cross this with you for a moment. That is, you have chosen in your life to take on two extraordinarily dominant paradigms that have a lot of what I would call intellectual sclerosis associated with them, one of which is autoimmune disease, which you very gracefully talked about—this shifting paradigm that maybe it's a two-way street and the environment and genes interact in a way that can go both ways, meaning remission plus progression. That's a pretty remarkable concept in itself. And now you have crossed another bridge, and I'll just cite three recent papers that you are an author of that illustrate this bridge. It's part of this overall theme, but it is certainly taking on another level of visibility, and those three papers include your 2012 paper, "The Expression of Caspaces is Enhanced in Peripheral Blood Mononuclear Cells of Autistic Spectrum Disorder Patients."[3] That appeared in the Journal of Autistic Development and Disorders in 2012. And then the paper, "Gastrointestinal Conditions in Children with Autistic Spectrum Disorder: Developing a Research Agenda."[4] That was in Pediatrics in 2012. And then most recently, "Cannabinoid Receptor Type 2 But Not Type 1, is Up-Regulated in Peripheral Blood Mononuclear Cells in Children Affected By Autistic Disorders" in the Journal of Autistic Development Disorders.[5] This is—as we both know, and you are a pediatric gastroenterologist, so you know it much better than I—a very colored area as a consequence of the work of Andrew Wakefield, who has gotten himself obviously into some muddied water over his purported discoveries in England of this relationship between what he called ileal nodular hyperplasia and autistic spectrum disorder. I'm wondering, as you have moved across this bridge with such precision and such science, how you have managed the legacy of what might be considered colored information in this area.

Autism and the Gastrointestinal Tract: Controversy Put Research on Hold for Years

AF: Well, Jeff, you put that in a very polite way, but this is a very heated, extremely controversial field of the role of the gastrointestinal tract in autism spectrum disorders. Again, this was an unfortunate situation in which it doesn't matter which part of the fence you are on. It created tremendous confusion in the field—distrust on the topic—and who ultimately paid the price have been the patients. We saw a deceleration of science that really put the entire field on hold. What are the facts? The fact that I don't see anybody dispute is that there is an axis that puts in touch and cross talks gut with the brain. That's pretty much a concept that everybody now accepts; there is a brain/gut axis. This applies not just to autism, but to schizophrenia, it applies to multiple sclerosis, and so on and so forth. The basic science to explain the mechanisms that are engaged in a situation in which you have an inflammation of the gut that eventually will affect the behavior of individuals, and now specifically there is concern about the autistic kids. Again, I was pretty much brought into the picture by force by some people in the autistic community because they honestly appreciated that there is some involvement of the gut. There has been this unfortunate situation that I don't think we need revisit, and they decided, rather, to ignore the possibility the gut has anything to do with autism. It was to start all over again in doing this right. And therefore with the understanding that my expertise in autism is extremely limited, and I mentioned this right away to

these people that asked me to give my opinion, I had the opportunity also, in a very unbiased way, to take a look at the situation and I find it is fascinating. Everybody agrees that autism is a situation that you can develop via different links. In other words, metabolic disorders, genetic problems, you can have metal exposure, I believe that vaccination can be involved, definitely food intolerance, and so on and so forth. So everybody agrees there are different paths that can bring you to your final destination, yet everybody was looking for a single magic bullet that will fix them all. That, to me, is counterintuitive. There are different theories, not mutually exclusive, why people eventually develop autism through a GI-initiated process. For example, for food intolerance, going back to gluten. People believe that some of these fragments are not digested that mimic endorphins that cross the intestinal barrier and cause leaks, and go through the blood-brain barrier, and interacts with the receptor endorphins and make these people change behavior and then with specific genetics translate into autism. There are theories about what is called neuroinflammation. Same first step: you eat gluten and undigested fragments will create an immune response and then the cells that fight this enemy are activated, so they can create inflammation, but somehow they are programmed to leave the intestine and to reach, as the final destination, the brain, and on specific regions, create neuroinflammation that leads to autism. This second theory now is the one I have been following more closely because the results of the papers that you just mentioned seem to point to this new inflammatory theory I find fascinating, absolutely fascinating. And again, the instigator can be gluten, it can be a virus, it can be a bacterium, it can be a metal, whatever, but somehow these new cells, on the battlefield of the intestine, they are supposed to protect us against these enemies, but they are programmed to go to the brain. Who makes this decision? How they are programmed? Why do they go to one part of the brain and not another? And why there are different outcomes, because the same mechanism for autism applies to schizophrenia and depression and chronic fatigue syndrome. These are the same cells that go there—maybe different regions of the brain—and generally have a different clinical outcome. I find this effect of neuroinflammation instigated by response of the level of the gut-immune system extremely fascinating, and very, very difficult to tackle. But I think you need to go step by step and start to ask specific questions and see if you can have specific answers.

JB: That was…once again, you have such an extraordinary gift in summarizing and bringing together a huge amount of information in a very concise way. I just want to pass on once again our deep respect and admiration for your courage. I think this is not an easy area politically to work in. It requires the best of science to convince sclerosed minds that there may be something on the other side that they didn't take advantage of trying to understand and were unconscious to. I'm thinking of a psychiatrist (MD, PhD) from Belgium who has published extensively about work associated with depression, and chronic fatigue syndrome, and fibromyalgia related to gut barrier problems and metabolic endotoxemia, or Patrice Cani and Nathalie Delzenne at Catholic University of Louvain, the work that they show with endotoxemia and an association with neurotoxicity.[6],[7],[8] There is an emerging family of colleagues that you share the universe with that are all very courageous. Good scientists, good observers, that are creating the new medicine. Just as one small observer in this world I want to give thanks to you for what you're doing, for your team. I hope you will thank them on behalf of us at Functional Medicine Update, and continue with the extraordinary work, because it is the quality of the work that will ultimately change the people's minds.

AF: Jeff, thank you so much for your kind words, and again, on behalf of the entire team we will appreciate your help and support and the fact that you see the value of what we are doing. I want to stress, once again, the entire team works towards the goal to improve quality of life for people, nothing else. As far as we reach those goals, even if we have been wrong, so be it. We will be delighted to say that we

were wrong so long as we move the field forward.

JB: Thank you, Dr. Fasano. We wish you the very, very best and be assured we're going to keep in close touch with what's going on with your laboratory.

AF: Thank you so much

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