



## A Grain of Truth: The Gluten Summit

Presenter: Dr. Alessio Fasano, MD

### Why Creating the Healthiest Intestinal Environment Possible Can Arrest Your Vulnerability to the #3 Cause of Getting Sick and Dying

**Dr. O'Bryan:** Hello, everyone! Welcome to another edition of A Grain of Truth: The Gluten eSummit. I am absolutely honored to be here today with Dr. Alessio Fasano, the world-renowned pediatric gastroenterologist and research scientist. Dr. Fasano completed his medical training at the University of Naples in Italy. In 1993, he founded the University of Maryland School of Medicine's Division of Pediatric Gastroenterology and Nutrition.

Ten years later, he published the groundbreaking study in the *Annals of Medicine* that established the prevalence rate of celiac disease at 1 in 133 people in the U.S. This was groundbreaking and woke everyone up that celiac disease was much more common than we thought.

In 1996, Dr. Fasano founded the Center for Celiac Research at the University of Maryland, the first celiac center in the United States. Currently, he is at Mass General Hospital for Children where he heads the Department of Pediatric Gastroenterology and Nutrition. Clinical and research work at the center has helped to identify the new disorder of non-celiac gluten sensitivity as a condition on the spectrum of gluten-related disorders.

Dr. Fasano leads a team of researchers across nine countries, and enjoys research partnerships with institutions around the world. He has published more than 220 peer-reviewed papers. And, he has received numerous awards for his translational science and other achievements. He's been named one of America's top doctors by Castle Connolly for five consecutive years, and was a 2005 finalist for the NIH Director's Pioneer Award.

In the year 2000 Dr. Fasano's team discovered zonulin, the molecule which regulates intestinal permeability, also known as leaky gut. Their groundbreaking research has linked an overproduction of zonulin to the development of a series of autoimmune diseases, including type I diabetes, celiac disease, and multiple sclerosis.

Dr. Fasano, thank you very much indeed for joining us today!

Dr. Fasano, our first question is about the digestibility of gluten in humans, especially for those who do not have any recognizable symptoms when they're eating gluten. Is it a problem for them?



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**Dr. Fasano:** Well, the [2:30] matter of fact is that, indeed, gluten is not digestible by any human kind. So, this is due to the fact that the structure of this protein is rather unusual. And, to make a complicated story as simple as I can, the way that we make use of our foodstuff is to first of all ingest it, of course. And, then we need to digest it. And, we have specific tools that we use to digest foodstuff. They're called enzymes. They are the sort of scissors that need to cut these long chains in small pieces first, and then other enzymes will complete the process by pulling off of these chains the single elements that are called amino acids.

So, again, if we want to use a parallel, proteins are sort of pearl necklaces that need to be broken. And, then, when they're broken, they are cut in pieces. And, then, the single pearls are peeled off so that we can make use of them by absorbing and using them for our own purposes.

We cannot do this completely with gluten because the composition is strange. It's unusual. It's enriched with two amino acids called proline and glutamine. And, the sequence of these amino acids aren't recognized by the scissors to break these proteins. It's very unusual. And, that's the reason why we do not have these enzymes that can completely break down gluten.

Now, saying that, the consequence of this poor digestibility of gluten may be absolutely nothing. And, that happens to the vast majority of us. We eat gluten. We do not digest it. And, pretty much, we are symptom-free. And, then there's the minority--and, here, we can discuss about numbers--that may have consequences leading to symptoms.

**Dr. O'Bryan:** With the proline and glutamine, these amino acids that are locked in so tight that our digestive enzymes can't break them down thoroughly, has this always been the case? Or, is this the result of the changes in the wheat from our agricultural industry in the last fifty years?

**Dr. Fasano:** No, it's been always that case because, again, we need to appreciate that we did not evolve [5:00] to deal with these proteins. As a matter of fact, for almost 99.9% of humankind's evolution, our ancestors have been gluten-free. Gluten came into the picture only 10,000 years ago with the advent of agriculture when our ancestors changed dramatically the lifestyle from nomadics--i.e. chasing foods by going after migration of animals and seasonal crops--to settlers when they started to domesticate animals and crops. And, that's where they started to play with grains--quote, unquote engineered grains. And, in this playing, gluten-containing grains like wheat, rye, and barley came into the picture.

So, the characteristic gluten has been there from the very beginning. As a matter of fact, it's really this enrichment, this proline and glutamine, that have been always part of the organoleptic, the gluten, which makes the gluten-containing grains so unique because



gluten gives the elasticity. And, other organoleptic characteristics of these grains that are not shared by other grains. So, that's the reason why if you want to have a good bread or you want to make pizza or pasta, you can't do it with grains other than the ones containing gluten because they have those kinds of characteristics.

**Dr. O'Bryan:** Yes. So, there are those out there that are proposing that the earlier varieties of wheat that were grown--the emmer variety and things like that--they may be more easily digested. Or, if you sprout the grains before you bake with them, they may be more easily digested. Have you seen any evidence of that?

**Dr. Fasano:** Well, actually, I'm not an agronomer. But, if I have to point to an expert in the field, there's been definitely a change over the centuries of the gluten-containing grains. And, it's more than a change in quantity rather than quality. So, in other words, the amount of gluten per dry weight of the grain has been increasing over time. And, that makes, of course, the digestibility of more recent grains much more difficult than the previous grains.

In other words, whoever studied agronomy and evolution seems to suggest that the amount of gluten [7:30] in the wheat that Greeks and Romans were using, for example, to make beer or for panification, had a concentration of gluten that was much lower than the grains that we have now. Now, gluten represents the largest percentage in the protein component of wheat. Roughly thirty or forty percent of the dry weight is all gluten while, a few centuries ago, we were talking about half of it.

**Dr. O'Bryan:** Oh, my. Yes, yes. And, I've heard the theory that with young couples who are gluten sensitive--perhaps one is a celiac and the other notices they feel better without gluten, or just one being a celiac--of the parents, they're concerned about introducing gluten to their children.

We know that there's a timeframe within which it appears to be that you can increase the child's defenses so that they're not as likely to develop celiac disease, at least in the years that have been monitored: five years, ten years out. Is there any validity to the premise that if and when a child, a toddler or an infant is introduced to gluten, if they were introduced to the earlier forms of gluten, it may be less stressful to their systems and enhance their immune response so they're protected?

**Dr. Fasano:** Well, there's a large body of research in this field. And, it's far from being settled because these are complicated studies because to answer the key questions--when it's safe to introduce gluten, and what is the consequence of introducing the gluten at a certain period of time--requires prospective longitudinal studies. They have to be for decades. And, we're in the making. We're not quite there yet.

What are the facts? The fact that we know for sure is that if you introduce gluten too early, it's detrimental. And, this was, unfortunately, the consequence of a sort of natural



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experiment that was done in the seventies in Scandinavia, in Sweden. And this was the consequence of business [10:00] changes of operation from a very famous formula maker that will stay unnamed. At that time, to find a niche of the market, this company decided to introduce what they called a fortified formula.

So, they stressed the concept of that, and the needs to help the kids transition from a milk-exclusive diet to a solid diet by introducing this fortified formula. So, the idea was from zero to two months, the baby is fed either with breast milk or the formula milk. From two until four months, [the babies] will be introduced with this fortified formula that will be a formula with wheat in there. And, then, from four months over, start the baby food.

What happened in that time in that generation, the prevalence of celiac disease went seven to nine-fold higher. So, it was one percent in the generation before. And, up to seven to nine percent in the next generation. When the co-respective CDC in Sweden realized the possibility of this coincidence of introduction of this formula with these epidemics, they retired the formula. And, the following generation of kids did not have that high percentage. It went back to one percent. So, that is telling us if we introduce gluten too early, we'll increase dramatically the risk to develop celiac disease in genetically predisposed kids. That's for sure.

Then, there is another theory, mainly supported by studies done by the Colorado group that followed kids at risk for celiac disease that suggested there's a window of opportunity that if we introduce gluten between four to seven months, we increase the chance of tolerance to gluten because based on the data, introduced earlier than four months or introduced later than seven months, both carry higher risk.

That kind of window has never been confirmed by other studies. [12:30] As a matter of fact, there are now studies that propose to postpone the introduction of gluten until after the first year of life. And, the idea is to give the immune system time in the gut to mature well enough to deal with this strange protein.

And, there are several studies that have done that, including our group. They've followed 700 kids from birth at risk of celiac disease. And, one thing is for sure indisputable, the data that we have so far seems to confirm the idea that there is no increased risk by postponing the introduction of gluten whatsoever actually. The kids who introduced gluten later, they have a lower risk to develop celiac disease for a certain period of time. So, in other words, compared to kids who introduced gluten at four or six months of age as currently recommend by the American Academy of Pediatrics, the kids that delayed interaction of gluten seem to be at a lower risk to develop celiac disease.



However, we are too early in the follow up. And, as a matter of fact, now that we're roughly five or six years of follow up, we see the two curves start to come together. So, it's possible that rather than prevent celiac disease by introducing gluten later, we delay the onset of the disease. That is still a great outcome because you increase quality of life for the time being.

I don't think--at least I'm not aware--of studies in which kids were introduced to ancient grains rather than modern grains to see if this will eventually be beneficial in protecting them against reaction to gluten.

**Dr. O'Bryan:** Yes, well, and the theory of if a parent is going to be introducing grains, does the theory of using more ancient grains seem valid? Or, would there be any risk in using more ancient grains?

**Dr. Fasano:** Oh, I don't think so. I don't think that there's any risk. I want to clarify something. Gluten is, nutritionally speaking, useless. We don't need that. And, again, we evolved as a species without gluten.

**Dr. O'Bryan:** Yes.

**Dr. Fasano:** So, there is no risk to avoid gluten or to use ancient grains. There is an inconvenience, of course. [15:00] You have to find foodstuffs that contain these different grains. But, other than that, there is no harm in using these ancient grains. Now, again, these ancient grains supposedly have a lower content of gluten. So, the gluten load probably will be reduced. If this is beneficial or not, honestly, I don't have any data that I'm aware of, at least to support the notion that this can be beneficial or not.

In theory, I think that, again, if we believe that the amount of gluten--not just the quality, but also the quantity of gluten--can drive a response that leads to a clinical situation like celiac disease or gluten sensitivity and food allergies, then it makes a lot of sense to use low gluten-containing grains.

**Dr. O'Bryan:** And, a comment that I'd like to make regarding your observation that if we are delaying the development of celiac disease for some of these kids, if that turns out to be the long-term follow up, then the benefit has been the quality of life in those years.

But, also, for our parents, the development of our tissue, that the way the baby develops, during those years where they have not developed celiac disease, they don't have that inflammation going on, you only can develop a stronger, healthier child at eight months, nine months, ten months, one year, two years, three years out. Their bones are growing stronger. Their nerves are growing stronger. It would seem their brain would develop more to its optimal so that one of the benefits may not only be the



quality of life during that time, but also the quality of the tissue the child is developing through the rest of their lives. Would that makes sense?

**Dr. Fasano:** That's intuitively the case. I mean, again, the goal here, particularly in pediatrics, is to prevent rather than treat. I mean, we do this routinely even with commodities. We change oil in the car every three thousand miles, even the car runs fine. And, the reason why we'll do that is because we don't want to blow up the engine. So, if we treat so well our cars, we should treat ourselves well, as well.

So, preventative medicine, it's definitely a must, not only because we'll improve the quality of life of people—and [17:30] that is our mission as the health care professionals—but because also for health care costs, it's much more cost effective. And, I don't think that, at least in the forthcoming future, we'll have the chance to make a choice between interventional medicine and preventative medicine. We've got to go with preventive medicine.

And, to go back to what you just said, it's intuitive that if you prevent a fit of chronic inflammation, no matter what it is, of course you would love these kids to develop healthy and not having problems during their development.

**Dr. O'Bryan:** Yes. For our general public audience that's listening, this next question...For the healthcare practitioners listening, the thousands of healthcare practitioners, most, if not all of them, know of your pioneering work in introducing us to the impact of intestinal permeability and what the possible impact of intestinal permeability is.

For the general public, the intestinal permeability...Well, I'll actually ask you first. Could you tell us, what is intestinal permeability?

**Dr. Fasano:** It's one of the key functions of the intestine that I probably think has been the most overlooked over human biology. So, we always were under the impression that the key function of the intestine is to digest and absorb foodstuffs. And, that, of course, is an important function. But, it's not just that. It's much more than that. If we just pay attention to what nature has done in engineering this wonderland system that is the gut's intestinal system, you start to wonder why the anatomy and the physiology is built in that way. And, you start to see, sure, this is a long tube with an amplified surface. That means we want to interface with the environment as much as we can.

And, again, the simplistic interpretation is that we want to digest and absorb in an efficient way the foodstuff that comes through. But, also, you start to see the fact that it is a single-layer cell, that just underneath that, the most sophisticated and abundant immune component [20:00] in our body because the intestine has the largest



immunological components. And, then you start to see there is a very sophisticated neuroendocrine network to control all this.

And, when you put all this together, when you connect the dots, you start to wonder, "Well, what else besides digesting and absorbing foodstuffs is the intestine doing?" The key function is to interface with the environment and eventually exchange information, including molecules from the environment that comes in in a very tightly coordinated and controlled manner. And, the bottom line, the modern biology seems to suggest that the state of health or the state of disease is the combination between what we are--meaning what genetically makes us, the way that we're engineered--and the environment that's around us.

And, we knew this for a long time. Evolutionary biologists, they knew that. Clinicians, they knew that. So, you can take identical twins. They have identical genetics. You split [them] at birth. And, one will be grown up in the North Pole and the other one in the Equator. At the end, these kids, even if they are identical twins, they will look totally different, meaning that, again, we are whatever we are at the component of these two worlds: the genes that we're born with and the environment that surrounds us.

And, the gut is the point of entry in which these two elements, they really meet. And, the way that, again, this exchange happens, it really is totally controlled by the permeability of the gut. They allow--if and when allowed--molecules to come through. And, on a specific genetic background, this brings us to the outcome of the overall picture of what, biologically, we are.

And, if everything goes fine and this traffic is tightly controlled...And, again if you look at what nature did, you really realize that this is an extremely important function of this intestinal permeability, we stay in a state of health. But, if this tightly-controlled trafficking is, for whatever reason, **[22:30]** jeopardized because of an infection, because of a change of the composition of bacteria in our gut--i.e. dysbiosis because we're abusing antibiotics--because, again, we're exposed to pollutants, chemicals, or genetically engineered foodstuffs, in other words, stuff that will prevent perfect function, we will pay a price.

So, we don't have this tightly-controlled trafficking anymore. But, this uncontrolled trafficking of these molecules. And, depending who we are, on what kind of genetic background we have, we can develop different problems. For example, we can develop food allergies if we are skewed to develop allergies. We can develop autoimmune diseases. We can develop chronic inflammation that can lead to a stroke, Alzheimer's, you name it, cancer. And, all this depends, again, on who we are genetically speaking, and what kind of environment is surrounding us.



So, I think that to make this in even more simple terms, when we're born, and, therefore, we have the entire genetic potential, we are like a very precious single marble block. But, what is going to end up on this marble block in terms of what kind of sculpture, it depends on the environment. So, it can be an environment that you can become the painter Michelangelo's David. Or, you can be in a different environment and the outcome will not be so wonderful. And, that's pretty much the story.

**Dr. O'Bryan:** Well, that's a beautiful analogy. I just came back from Florence and had an opportunity to see, once again, the statue of David. And, it's such a beautiful story that there was this large block of marble that a number of other sculptures had said was faulty and could not be used.

And, one craftsman, one sculptor, said, "I see David in there." And, then, went after it. And, this is what we want. I'm thinking of this for our parents, that when you have newborn children and you're raising your children, the environment that you expose your children to [25:00] has a direct impact on how they develop. So, we always want to be thinking about the quality of our foods and the environment that we're putting our kids in, and ourselves. That's a beautiful analogy.

**Dr. Fasano:** What seems to be a vision or theory is confirmed by factual or epidemiological observation. For example, we're in the midst of an epidemic of autoimmune diseases like asthma, diabetes, MS, rheumatoid arthritis, celiac disease. And, these epidemics have been taking shape in the last forty or fifty years.

If, indeed, the state of health or disease is the consequence of this interplay between genes and environment, this is a too short period of time to blame the genetic changes to be responsible for these epidemics because the mutation of genes takes centuries, not years. So, definitely, what we are observing is the fact that we're changing our environment so fast that we cannot adapt. And, we're paying a price.

**Dr. O'Bryan:** Yes, one of the guests we'll have on the show is Dr. Aristo Vojdani, a PhD immunologist, who will be talking about the hygiene theory and what's happened in the last forty or fifty years and how that may be impacting on the environment of our intestines and the potential development of autoimmune diseases.

A few of the papers that you have published have suggested that a rational approach in addressing autoimmune diseases is to look at the intestinal environment, and create the healthiest intestinal environment possible. I believe one of your papers said that you can arrest the development of autoimmune diseases by addressing the gut and healing the gut.

Is that still a position that you would agree with these seven years later?



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**Dr. Fasano:** Well, in these seven years, actually, what was just a working hypothesis became much more tangible. So, the idea that I put on the table a while ago was that, again, the equation to develop any kind of immune-mediated disease, particularly autoimmune disease, calls for a third element besides the genes that you are born with, besides the environment, [27:30] there's also this third element that is the battlefield when these two things encounter each other. And, they interact in the intestine in particular, again, gut permeability.

So, the idea was if you have the genes that make you predisposed to this condition within the wall of the city, so to speak, so, in our body. And, then you need some instigator that comes from the environment--they are outside of our body--the two need to be physically interacting in order to develop this clinical outcome that can be, again, autoimmune disease, cancer, whatever. But, under normal circumstances, physiologically speaking, the intestine is built to prevent this from happening because of this formidable barrier function to keep bad guys at bay outside our body.

So, again, if you'll allow me an analogy, imagine these twelve feet or fifteen feet of single layer cell from the top to the bottom that you can compare to the Great Wall. A single layer of cells. And, again, the Great Wall was built to keep the enemy outside. And, once in a while there are checkpoints in the wall that are doors in which you can allow, under very tightly controlled surveillance, people to come within your city. And, these checkpoints in the intestine are called tight junctions. They are the structures in between cells. They are a sort of doors.

If, again, these checkpoints they work fine, then, you don't have an invasion of enemies coming within the walls of the city. But, once something goes wrong, when there is a breach of this checkpoint and, therefore, there is a loss of this barrier function, then there is an uncontrolled passage of these instigators that can eventually take over and create damage within the wall of the city. That's pretty much the concept that was put seven years ago.

Of course, the debate was extremely hidden because the vast majority of the establishment was skeptical about this idea because it went back to this leaky gut theory that over the years had been kind of vilified, [30:00] particularly by complementary and alternative medicine doctors because it was claimed it was a response to so many things, but it was not scientific ground about it, that's the reason why at the beginning we were highly, highly criticized to be not evidence-based, not scientifically sound, and so on and so forth.

But, the theory was based on a absolutely--I would say--indisputable paradigm that was...Okay, if you need to have an instigator that will lead to autoimmunity, and we know that these instigators in general are proteins or fragments of proteins because that's what the immune system can react to, under normal circumstances, if the



checkpoints are working fine, there is no way, there is absolutely no way that these large molecules can come through. So, something must be wrong at these checking points. And, that's where the science that we did accumulated over the years.

And, interestingly enough, more and more of this skepticism has been lifted off by evidence that suggests that, indeed, this third element that is the intestinal barrier function, is an integral part of the equation. We know now because the human genome and the capability to look at specific genes, we know there are some genes that control gut permeability, they are an integral part of the pathogenesis of many inflammatory diseases.

We know that, again, now we start to have animal models and even clinical trials in humans, that if you fix the gut barrier function, leaving the other two components behind, either genetic predisposition and exposure to environmental triggers, you can treat autoimmunity. And, I can go on and on and on.

**Dr. O'Bryan:** Yes. Yes. Well, I'll just take a moment to commend you and thank you for, as is true with most pioneers, you have to move through the bleeding edge to become the leading edge. And, thank you for your courage to stay in there with this one because I know it's in your heart and you believe it so sincerely. And, it's turned out to be right on the money.

For our general public listening, just a point of clarity, we talk about the genetics. And, that's the deck of cards you were dealt in life. And, you can't do anything about that. And, we talk about the environment. Now, for a point of understanding, what is the primary [32:30] source of environmental insult that we're talking about here, the primary category of environmental insult?

**Dr. Fasano:** For autoimmunity in general?

**Dr. O'Bryan:** For intestinal damage in general?

**Dr. Fasano:** Well, from what we understand, the key elements that can really change the physiology of how the intestine works is the composition of the bacteria that live within the intestine, what we collectively call the microbiota. There was a complete black box. We had no idea of what we were talking about. And, now, I believe with technology, they allow us to really have a deeper understanding of the complexity of the microorganisms that live within our intestines. And, we appreciated that we are living with a parallel civilization.

So, in other words, there are two different worlds. They're stuck together from birth until we die. And, they are necessary to each other. In other words, we know that without the bacteria in our guts, we will be in major trouble. And, we know this by experimental



models in animals and so on and so forth because, mainly, one of the key functions of this microbiome--that's the technical term of this parallel civilization--is to help the intestine mature its function, particularly the immune function. And, without that, we develop inflammation. So, we need bacteria.

And, it's also so obvious, though, that, again, this is always happening. People, they are living together as neighbors. You can live in peace or you can have disagreements. So, if you live in peace so that this cohabitant is mutually beneficial, we stay in a state of health. If, on the other hand, we have frictions and disagreements, then there is a fight. And, fights always have collateral damage that, in biology, we call inflammation.

Now, again, with the technology that we have right now, we realize, one, that when we're talking about the bacteria in the gut, i.e. the ones that we can cultivate by putting the stools in a culture, it's only one percent of what the actual complexity of the bacteria that are in the gut. Ninety-nine percent we cannot culture. [35:00] And, the wealth of bacteria there in the gut is roughly 1,000 to 1,200 different microorganisms that live at any given time.

If we're lucky, if we're born from a natural delivery, we inherited this wealth of bacteria from our mother. And, because, again, those bacteria were living in peace with our mothers, most likely they will live in peace with us because their genes, the microbiome, and our genes, the human genome, they are compatible. And, therefore we can work in symphony.

If, on the other hand, you are born by c-section, all comers--bad guys and good guys--can come in, some that will live in peace with us and some that are more belligerent. And, therefore, you can develop problems. We know already that if you are born by c-section, the chance to develop autoimmunity like celiac disease or type I diabetes is three or four times more.

And, the other thing that is pretty obvious now is that, again, when the human genome was complete, we realized that we are genetically extremely rudimentary as a species. We are made only by 25,000 genes. If you compare it to, I don't know, a worm, the ones that live under the ground, they have 90,000 genes. So, they're much more complicated than we are. Yet, I believe that we don't have to argue too much that worm and human beings, they have different levels of sophistication in terms of what they're capable to do.

So, where does our sophistication come from? It comes from the fact that we really are made by two genomes. The human genomes that's fixed, you cannot change. If there's a defect...Let's say they are genetically skewed to develop cancer or celiac disease or any other problem, you can't trade in. And, then, the microbiome that is 100 times more complex in terms of genetics, that will really affect how our genes are expressed and when they are expressed and so on and so forth.



And, all this to say this is an evolutionary concept that we just realized by some of the studies that we just published is that even if you're genetically skewed to develop these problems, it's not destiny that you will. It depends on the microbiome. [37:30] And, the microbiome composition is highly, highly influenced by the environment. First and foremost nutrition because these bacteria, they eat our leftovers. But, also, pollution, chemicals in the environment, radiation, stuff that we never, in other words, have seen before. And, I believe that, again, these epidemics that we're talking about--and you can discuss more with a colleague with the hygiene hypothesis--is really pinned down to the change in the composition of the microbiome due to all this environmental stimuli that eventually will put us out of balance. And, we'll create, again, this collateral damage of inflammation.

**Dr. O'Bryan:** So, thank you for that eloquent answer. So, for our general public, the environment we're exposed to impacts directly on the good bacteria in our guts and the colonies of good bacteria. And, the first and foremost primary environmental influencer is the food that we eat, the selections of food. Now, there's also radiation and toxic chemicals and toxins in our water. But, the foods that we select on a daily basis have a dramatic impact on the development and maintenance of the healthy bacteria in our guts.

**Dr. Fasano:** Yes. Of course, there are all sorts of elements. Probably the second most important is the use and abuse of antibiotics. As a matter of fact, this epidemic of autoimmune disease coincides with the introduction of antibiotics. Antibiotics is like dropping a bomb on this village. And, some of the bacteria, the ones susceptible, will be eliminated. And, the others, they are not susceptible, will stay. And, they take over. And, with this imbalance, of course, you have bullies in the neighborhood that will create problems, for sure.

**Dr. O'Bryan:** Yes, yes. Unfortunately, all of us are exposed to antibiotics whether it's by prescription or not. Some of us know that our farmers now spray their vegetables with antibiotics. There are many ways. The animals are given antibiotics. And, it may trigger through into the products that we get from our animals. There are many different sources by which we're exposed to this, which suggests that we [40:00] always want to have a little bit of vigilance about how we're feeding the bacteria in our guts. Our food selections, our environmental selections, what are we putting in there? Can we have a little bit of consciousness about putting supportive foods for good bacteria into our guts?

**Dr. Fasano:** That's right.

**Dr. O'Bryan:** Dr. Fasano, you have a marvelous quote that has made so many laugh out loud when they hear it. We've known for years, the studies have told us, that the gold standard in the diagnosis of celiac disease is a positive endoscopy biopsy demonstrating that the microvilli, the shags in the intestines, have worn down.



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Your quote says that you're not so sure that it's really gold. It may not even be silver or bronze. That's a marvelous quote! So, my first question in this area is can you differentiate between the celiac disease and the celiac condition?

**Dr. Fasano:** Yes. When you talk about celiac disease, nowadays, we define it as the autoimmune reaction to gluten. So, really, you attack your own body. And, that's the reason why, until the recent past, we were so fixated that to make the diagnosis, you have to have an endoscopy with a biopsy showing this autoimmune insult. That's how you make the diagnosis. And, again, in the past, we had no alternatives because we had no good tools to make an informed and specific diagnosis of celiac disease without having the biopsy done.

This is not a trivial diagnosis because the consequence of diagnosing somebody with celiac disease is to recommend a gluten-free diet for life. And, a very strict gluten-free diet. So, that's the reason why I want to have 100% certainty.

Personally, when we talk about celiac disease versus celiac condition--and this is another crusade that we embraced a long time ago--when you talk about disease, it's intrinsic the concept that something is wrong. That's the reason why you call [it] disease. Well, because celiac disease is the only autoimmune disease for which we know the trigger, because we don't know what makes [42:30] people sick with diabetes or MS. But, it's indisputable: gluten is the environmental trigger. And, because we know that, again, this trilogy of necessary ingredients to autoimmunity involved genes that you're born with and the environmental trigger and this breach of the intestinal barrier.

We know, also, that all three are absolutely necessary to develop it. If you take one of the three out of the picture, you do not have the recipe for autoimmunity. And, indeed, going gluten-free is exactly the way that we treat people with celiac disease. And, this revolutionized the entire field of immunology. Particularly the experts in autoimmunity they were convinced that there was a way of no return. There's nothing that you can do when you develop autoimmunity because it goes on automatic. So, there is no dependency on this environmental trigger anymore.

Celiac shows otherwise. It shows that if you somehow could identify the environmental trigger, eliminate it, you may eventually stop the process of this autoimmune ongoing attack. And, as a matter of fact, when you go on a gluten-free diet, if the diagnosis is correctly done and on time, the consequence is that the patient's symptoms will go away. The autoantibodies that we use for diagnosis will go away. And, the insult of the gut, this autoimmune insult, will go away.

So, in other words, going on a gluten-free diet, this individual is undistinguishable from anybody else in a state of health. So, I don't know why we should keep saying that this individual is affected by celiac disease. At that point, it's a condition. It will never go



away, of course, because if you reintroduce gluten, it will come back. But, it's a condition.

The other thing is, again, as synonymous as celiac disease was gluten-dependent enteropathy by stressing the concept you've got to have the damage in the intestine to make the diagnosis. But, now, so many times, we do an endoscopy. We go in and we can't find the damage, even if these people, they have the autoimmune reaction to gluten.

Why? Because sometimes the lesion is patchy. So, it may be that you take the biopsy in a place that's spared by the damage. [45:00] Sometimes, the pathologist cuts the piece in the wrong way so you cannot make the right call. Sometimes, the damage--even if it's unusual, but it happens--is more distal, and therefore, the endoscope cannot reach. And, that's the reason why I don't think that, again, we can talk about gold standard anymore.

**Dr. O'Bryan:** Thank you for that. What I considered a landmark paper came out in 2009 by Ludvigsson. Because in Sweden they have socialized medicine, they have records on everyone and their health. And, they've had the opportunity to look at hundreds of thousands of biopsy reports. And, in this paper in the *Journal of the American Medical Association*, they found 39,000 celiacs as defined by total villous atrophy. So, they had the enteropathy.

They found 3,700 that just had an increase in their blood markers. The antibodies were elevated, but they did not have a positive biopsy. And, then they found 13,000 that did not have positive blood work or positive endoscopy. But, they had increased inflammation in the intestines. And, they followed them for--I think it was 25 or 30 years--they looked to see what happened to these people.

And, they found that those that had been diagnosed with celiac disease--even with a gluten-free diet, with or without--they had a 39% increased likelihood of early mortality compared to someone that did not have celiac disease. Those that had positive blood work, but negative endoscopy and histology had a 35% increased mortality. That immediately raises the question of how critical is it that we have the visible, identifiable, villous damage before we institute a recommendation?

But, even beyond that, those that had just the inflammation--blood work was negative. Endoscopy was negative. They just had the inflammation--they had a 72% increased risk of early mortality. Almost double. So, the question is at what point should our practitioners, when would they be recommended [47:30] to consider taking action and make a recommendation of a gluten-free diet to their patients?



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**Dr. Fasano:** Well, again, that paper that you just alluded to, it's one of the most massive amounts of information that we have concerning celiac disease and overall risk of mortality. There is a misconception. Again, it goes back about the stringency and the necessity of the enteropathy. If we review what are the steps that lead to this inflammation that seems to be the key element--not the enteropathy, not the biomarkers of celiac disease, but inflammation--the steps are pretty straightforward.

One, you have to eat gluten. Two, gluten, as we know it, is only partially digested. So, if you don't complete digestion, those peptides can instigate inflammation if seen by the immune system. Three, the intestine leaks. So, somehow--and we know how now because there are fragments of this, some of these undigested fragments of gliadin and gluten can release this molecule that we just called a while ago that's called zonulin that can make the intestine leak--and, the stuff comes through. This happens to all of us. We all eat gluten. We all cannot digest. We all release zonulin. And, therefore, we all have this breach of intestinal barrier stuff come through.

Now, for the vast majority of us--and, again, I don't know the number, probably 70% or 80%--we can clean the mess and we will not have consequences. The remaining will have consequences that depend [on] who you are. The misconception, even in the world of celiac disease, is that when this encounter between the instigator and the immune system occurs, these cells that you can compare to sorts of soldiers, will get armed and will start to shoot weapons against this enemy that, technically, we call cytokines. These are chemicals that can destroy tissues, intestine included.

Now, another statement that I made many years ago is that the gut is not like Las Vegas. **[50:00]** What happens in the gut doesn't stay in the gut. So, some of these soldiers, when armed, stay there and start to fight the enemy there. And, the collateral damage is created inside, right in the intestine where you have the damage. Those are the classic cases in which you see the autodestruction and so on and so forth that are typical of celiac disease.

There are other people in which, not only some of these soldiers of our immune cells stay there--but for reasons that we don't know and from mechanisms that we're totally aware how it happens--some of these soldiers, i.e. immune cells, are programmed to leave the intestine and to go somewhere else. And, somewhere else means anywhere in the body. So, they can go to the joint, and you can have joint pain. They can go to the nerves, and create peripheral neuropathy. They can go to the skin and create problems. And, speaking of the skin, [it] is a classic example of how you can have an inflammation that does not involve the gut at all. The skin manifestation of celiac disease is called dermatitis herpetiformis. If you do a skin biopsy, you find the same collateral damage that we find in the intestines with people with classical celiac disease.



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Now, if you do an endoscopy of these people, roughly 75% of these people, no matter if they have GI symptoms or not, they have the damaged intestine. But, 25% have no damage whatsoever. In this 25%, 100% of the soldiers, once armed, they leave the intestines. So, they don't fight there. They don't create inflammation there. They leave the intestines, and they all go to the skin and create a problem there.

There are people that, again, they have no damage whatsoever in the intestine. And, these cells, they go to the brain and start to create inflammation in the brain. And, neural inflammation can be manifested in so many ways in celiac disease or other gluten-related disorders.

So, you see the complexity of the matter and how reductive it is to say, "This is a GI condition." The gastrointestinal tract is simply the battlefield where the first encounter between these enemies and our soldiers i.e. the immune system occurs. And, the way that the soldiers [52:30] behave--stay there, go somewhere else, create other collateral damage somewhere else--it's all dictated by our genetic makeup. That's the reason why genes are important.

**Dr. O'Bryan:** You say that we all will get intestinal permeability if we're exposed to gluten, if we have this environmental exposure to gluten. And, I had the opportunity to sit and hear you speak before. And, you differentiate between those that have celiac disease and what the likely impact is of gluten exposure, and those that have non-celiac gluten sensitivity, and those that have no noticeable immune response.

Can you tell our audience, all three categories, what the potential impact of any gluten exposure may be?

**Dr. Fasano:** Sure. Again, starting from the people that have no consequences, these are the conditions in which you eat gluten, gluten is partially digested, breaches the intestinal barrier by having cross talk with intestinal cells, get underneath this layer of cells, what we call within the wall of the city, so to speak. The soldiers see the enemy--i.e. the immune cells see gluten coming through--and they do their job. When there's something that does not belong to our body that we call non-self antigens, we'll eliminate that. And, again, the vast majority of us will go through this process. And, we're totally unaware it's going on.

If we are skewed to develop celiac disease as an autoimmune formal reaction, the first three steps are the same. We eat gluten, which is only partially digested. It breaches through the barrier, comes within the wall of the city. Now, these immune cells are meant to get rid of this enemy, and, therefore, fight against them, their weapons, however, by mistake. Rather than to fight the enemy, they start to attack their own body. And, depending on the target, you can develop different kinds of outcomes. In this case, the target intestine is destroyed. And, therefore, you develop celiac disease.



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In order to do that, you have to have the involvement and the coordination of the two major branches of the immune system. We have two ways that we fight enemies when we're exposed. [55:00] We have the first deployment of our soldiers, the one that goes right away to the battlefield, very light weapons because they can't carry huge weapons because otherwise we'll be not efficient. And, therefore, they can be on the battlefield right away. But, they cannot sustain a long fight. And, this branch is called innate immunity. So, they don't care what kind of enemies they are dealing with. They don't care about their sophistication. They just care that they do not belong to our bodies. And, they have the mission to get rid of it.

If they can, and, therefore you can get rid of this enemy, the story is taken care of only by this branch. But, if the enemy is resilient and will not go away, then this branch of the immune system cannot sustain at length this fight. And, they have to call reinforcements. They have to call the heavy artillery, the navy, the Air Force. So, they have to come up with big weapons. And, that is what we call adaptive immunity. They're phylogenetically more modern. And, it's much more sophisticated. But, this other branch of the immune system needs time to arm itself because it has to customize weapons against a specific enemy, what we call antibodies. So, they have to build weapons specifically for gluten. And, that takes time.

Celiac disease, like many autoimmune diseases, seems to be the consequence of miscommunication and miscoordination between innate and adaptive immunity. So, they can't coordinate this well. So, the adaptive immunity, the ones that really make these weapons, is wrongly instructed. And, rather than to build weapons against gluten, it starts to build weapons against its own body--in this case, the gut--and destroy the gut. That's the essence of autoimmunity in general, and celiac disease in particular.

There's another form of gluten reaction that is just recently described that it's called non-celiac gluten sensitivity, in which the defect is totally, exclusively in the innate immune branch. The adaptive immune, the ones that have the heavy weaponry that creates damage, is not involved at all. That's the reason why [57:30] in gluten sensitivity, you will never have the enteropathy. There is not going to be destruction of the intestines. There will still be inflammation. And, that's the reason why these people develop symptoms, but not destruction of the intestines. And, as you alluded to, the consequence of chronic inflammation in the general economy are not totally known. But, it's intuitive that you can have consequences in terms of life expectancy and well-being and so on and so forth.

**Dr. O'Bryan:** What is the overview that you ideally would like to see for an individual who does not have the genes for celiac disease, but either they've done a blood test and they have an immune reaction to gluten, or they've not done any tests, and they notice they just don't feel as well when they eat gluten? How would you like the world to



look at that overview of their body and its relationship to this environmental input of gluten?

**Dr. Fasano:** Well, again, the challenge here is that people that can develop symptoms when exposed to gluten--not on an autoimmune basis, not celiacs--they may develop symptoms like celiacs. They are very aspecific. You can have abdominal pain. You can have headaches. You can have a foggy mind. You can have chronic fatigue. You can have depression. You can have chronic headaches. So, you realize that it's very difficult to make the diagnosis simply on the clinical basis because there are 25,000 things that can create all this.

So, my strong recommendation is, first and foremost, until we find specific biomarkers to identify this entity, you need to make sure that you rule out everything else that can explain these symptoms. Let me make an extreme example. Let's say that you have, indeed, chronic fatigue, foggy mind, and a severe headache. And, you read that this may be gluten. And, you go on a gluten-free diet. But, actually, you have a brain tumor. And, you did not look into this. What dramatic consequence can you have about that?

But, if you've done your own work, you've done the MRI, everything has been ruled out. And, at the end of the day, nobody [1:00:00] can come up with an explanation why you have these symptoms, I believe it's very legitimate at that point--and only at that point--to consider a trial on a gluten-free diet to see if, indeed, is gluten the culprit? And, again, this is in view of finding biomarkers that will allow us, at the very beginning when you develop the symptoms, to check if you have gluten sensitivity so that you can go straight to the point.

**Dr. O'Bryan:** Thank you. A very rational approach. With the Oslo conference recommendations on nomenclature, we now have a recommended consensus on how to refer to the specifics and the different phases of gluten-related disorders for researchers, scientists, clinicians, the general public. We're all being asked to use the same language.

In this last March's issue of the medical journal *Gut*, Dr. Michael Marsh suggests that we reconsider the use of the word "chronic" with reference to celiac disease to the use of the word "permanent." Do you see the possibility that celiac disease may not be a permanent condition for some, and would take issue with that recommendation? Or, would you think that that is a rational consideration?

**Dr. Fasano:** Well, if we accepted, again, this is an autoimmune disease with a genetic component, and if we accept the concept that once you have these genes, they cannot go away, I believe that "permanent" is appropriate. But, again, I have also to say that contrary to what we believed before, even if you have the genes, it's not destiny that you develop that condition.



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And, again, this was a very shocking surprise to us that came to fruition when we completed a study that was focused on 3,000 healthy individuals. They were followed for 50 years. The purpose of the study was completely different. What we were trying to do was, we know that celiac disease can be clinically silent for a long time. And, our dogma at that time was in order to develop celiac disease, you have to have the genes, and you have to eat gluten. That means that when the two encounter each other--and that [1:02:30] always, 100% of the time, happens in the first year of life--that's when the autoimmune process starts.

Now, some people develop this soon after this encounter occurs. And, these are the classical cases that develop in pediatrics. Others will develop later on. And, we thought that this difference was due to a slow-paced, less aggressive immune system that would create the clinical mass of damage in a much longer period of time. And, therefore, you develop in adulthood.

We were shocked to learn that in the specific cohorts of adults, celiac disease doubled every fifteen years. It was 1 in 500 in the seventies, 1 in the 250 in the eighties, and roughly one percent in the 2000s. There were people that were able to eat gluten for many years--two ladies for seven decades--and stay absolutely healthy. And, then, after 70 years, they lost this luxury. And, they switched from tolerance and a state of health to disease. So, that raises two questions. What kind of tricks had these people been using to tolerate what is an indisputable instigator of autoimmunity? Because if we learn that, we have the Holy Grail of prevention of autoimmunity and inflammatory diseases. Unfortunately, this is going to be a very difficult task. I don't think that this will eventually be resolved in a short period of time.

But, the corollary of this means that even if you have these genes that make you at risk for celiac disease, not necessarily [do] those genes translate in disease. So, it is permanent. But, it's not a destiny. Many people may lead their entire lives without ever developing celiac disease. And this is a modern concept, what we call epigenetics.

And, the other question is what happens to these people that all of a sudden they lost this luxury? And, the most logical answer is the microbiome, the composition of bacteria in their guts, changed. And, now, they have bacteria there that fight with these neighbors, the host. And, these genes, [1:05:00] they were asleep. They were not used. They were expressed in certain ways. And, now, a touch, and all of a sudden you have the expression of a mix of genes. And, you have a perfect storm that leads to that situation.

In that case, once they're turned on, the condition is permanent. It will not go away. But, again, provided that you're gluten free, these genes will be the ones that determine that the immune system is building this weaponry, will not be creating any inflammation because there's no enemy to fight. And, therefore, the immune system will shut down.



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But, the concept “permanent” is pertinent because if at any time in your life, you will introduce gluten, sooner or later, this immune system will turn on again, and will fight again the battle.

**Dr. O’Bryan:** So, in the mechanism of development of the loss of oral tolerance and the development of celiac disease, we know that the peptide of gluten, the gliadin peptide of gluten, will bind to the enzyme transglutaminase. That’s one of the steps.

Is there any other mechanism that you are aware of by which the gliadin/transglutaminase complex may form besides in the mechanism that will eventually cause celiac disease?

**Dr. Fasano:** None that I’m aware of. The reason why this happens is because, again, the steps that will follow the ones that we described before-- i.e. gluten is only partially digested; it sneaks through the intestine and now it’s leaking, these fragments--the first thing that happens, again, is this innate immune system goes on the battlefield and starts to fight. And, the collateral damage will create the destruction of some cells. Not enough to have the enteropathy. But, some of the cells there within the wall of our city will be destroyed.

And, these enzymes that normally are inside the cells leak out. And, now, you have on the same battlefield, gluten that comes in, these enzymes that sit in there, and they form this complex. And, this complex [1:07:30]also creates a conformational change of gluten that, now, changed by transglutaminase, it’s a conformation that will be perfect to match on the docking station of immune cells. They are called HLA.

And, we know there are two forms of HLA: HLA-DQ2 and HLA-DQ8. They are absolutely necessary to develop celiac disease. And, the reason why that’s the case is because that’s the only way that the immune system can see gluten as an enemy because, again, these sort of antennas or docking stations, if you wish, in which gluten, once changed by tissue transglutaminase, needs to dock on. And, these immune cells--they’re called antigen presenter cells--now they take this complex and present to other immune cells that are called T-cells that eventually are the ones that will start to clear these weapons that will be used against our cells in terms of autodestruction of the intestines.

So, that’s how this whole chain of events occurs. And, the cells where these docking stations are that will activate the rest of the branch of the immune response are part of the adaptive immune system. And, therefore, again, this happens only if you develop celiac disease.

**Dr. O’Bryan:** Well, Dr. Fasano, I want to thank you very much for your generous allocation of time to us and answering our questions so openly and thoroughly. We look



forward to your work and your continued successes, and wish you much success and much support in continuing this effort in bringing to all of humanity the message of how to deal with this situation of gluten toxicity. Thank you very much, sir.

**Dr. Fasano:** Thank you very much, Tom, for having me. Bye.

\*\*\*End\*\*\*

Please note that Dr. Fasano's participation in the Gluten Summit is solely to provide factual information to the general public on gluten-related disorders. Dr. Fasano, the Center for Celiac Research, Mass General Hospital for Children and Massachusetts General Hospital do not endorse any products or sponsors represented at the Gluten Summit.



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