Dr. Fasano on the future of celiac disease

What he thinks about the biopsy, a pill, the economy, an increase in CD . . . and GF pizza

By Amy Ratner

SEVEN YEARS AGO, I sat down for an in-depth interview with Alessio Fasano, MD, director of the Center for Celiac Research, shortly after his landmark study that determined one in 133 people has celiac disease. There was great excitement at that time about all the things likely to happen now that it was clear celiac disease was much more common than anyone thought.

We met that time in his office at the University of Maryland School of Medicine in downtown Baltimore. It seemed fitting to be talking about the study and other cutting edge research not far from the celiac center clinic lab where much of the work was going on.

This time we talked over lunch in a noisy pizza parlor that has gluten-free pizza on its menu—something we could only have dreamed about in 2003.

Fasano, a prolific celiac researcher, writer, ambassador and advocate, had just returned from an ambitious trip to Europe where he traveled between Finland, Germany and his native Italy. In Finland, he donned a topcoat with tails and a very tall hat to participate in formal proceedings where a fellow researcher was defending his thesis on the role the biopsy plays in the diagnosis of celiac disease.

Fasano's own conclusion that the biopsy should no longer be considered the gold standard for diagnosis of celiac disease was an important topic in our interview. He and Carlo Catassi, MD, co-director of the celiac center, recently published an article in the *American Journal of Medicine* arguing for a new standard for diagnosis. Another key subject was the center's recent study that surprisingly found a doubling of celiac disease every 15 years since 1974. Fasano said the study, which showed celiac disease increasing as people age, suggests genes and gluten aren't the only things responsible for the development of celiac disease. Bacteria may also be involved.

News that the Food and Drug Administration is making progress toward finalizing a definition of "gluten free" also came up in the interview. A draft of the final version of the definition should be posted by the FDA by the end of the year, leaving public comment as the only other step left before the definition gets much-awaited final approval, Fasano said.

We also talked about a wide range of subjects—the role the economy plays in the advance of celiac disease research, how close we are to a drug to treat celiac disease, the gluten-free food market, a new

study into the role the introduction of gluten to children plays in the development of celiac disease, growing acceptance of gluten sensitivity, cross-contamination and more.

We did this while having a gluten-free pizza, hot from the fire of a brick oven. Fasano's evaluation of the pizza? "It's really ok," he said.

On other gluten-free topics he is much more prolific. Any extended discussion delves into advanced biology, market analysis, biotechnology, and clinical observations. Lest you think Fasano spends all of his time working on celiac disease, you should know he is also a former competitive swimmer, rides a Harley for relaxation, plays the saxophone and is the proud father of three children.

But when it comes to celiac disease, Fasano's bottom line, coming at the end of our interview, is simply put. "Honestly I appreciate that people are interested in treatment for those who have already celiac disease," he said. "Treatment is important but prevention—that would be something."

Several weeks after we talked, Fasano and the Center for Celiac Research got a huge boost toward the goal of preventing celiac disease when they received a $45 million gift from a grateful patient. It was the largest private donation in the history of the University System of Maryland.

Amy Ratner: During our last in-depth interview in 2003, we talked about a cure for celiac disease. Are we any closer now?

Dr. Alessio Fasano: Seven years ago a cure was just a theoretical discussion. There has been a steady increase in research, especially since 2005. In 2003, we knew it was technically possible. In 2010 there are 35 projects completed or in the pipeline related to the diagnosis, treatment or prevention of celiac disease.

Are we close to a cure or treatment? We are much closer than we were when we discussed this the first time. Now we see steps that are really possible. Keep in mind that whenever you talk about development of a tool, like a drug, you are talking about 10 to 15 years of study and close to a billion dollars. So it takes time and a tremendous amount of resources.

AR: Has the downturn of the economy had an effect on celiac disease research?

AF: The economy has had a tremendous effect. It put a slap on the brakes of a fast-track project. Look at the example of the two companies, Alba and Alvine, working on drugs to treat celiac disease. Alvine did studies that were completed in 2008 with 100 people. Alba's studies involve almost 500 people. They started to see efficacy and safety. In any other economic climate a big pharmaceutical company would have jumped in and bought these companies.

Right now both companies have to slow down and even stop because of the lack of money. It's scary. No one will take any kind of risk. It has been a travesty for the celiac community. Alba got to the very last step before the final trial of its celiac pill in only four years instead of the normal 15 years. Now it is dead in the water, just waiting. They had to downsize tremendously. Now we will have to see how the economy develops.

To me the pill will have the great advantage of peace of mind, that is all. I don't foresee it as an alternative to the gluten-free diet. I see it as complementary or supportive of the gluten-free diet.

AR: Would you have to take the pill every day?

AF: If you eat at home and know what you are doing, it's hard to believe you would contaminate yourself. But when you eat outside the home—at college, when you travel or go on vacation, then that's when you would use it.

AR: What about people who say they are perfectly healthy on the gluten-free diet and don't need a pill?

AF: That is something you can decide. Usually people fall into one of three groups. One says, "I am perfectly fine, I don't need the pill." The vast majority says, "I want the peace of mind. Usually I am fine but when I travel I want to have it." Then there is the other group, usually teenagers, who want the pill right away because they want to eat whatever they want.

AR: Has more of the change we've seen with celiac disease since 2003 occurred in the gluten-free marketplace than the medical world?

AF: Everyone who has experienced the changes in the marketplace is really benefitting from the changes in the medical world. Those who are newer to gluten free may not be aware of what the medical world was, say, five years ago. The awareness of celiac disease was so low, it took a long time to be diagnosed, and even when you were diagnosed, you knew more than your physician. When you know this, you realize there has been a tremendous change in the medical arena. People are benefiting from the efforts of the centers and others to increase awareness.

We went from a situation where celiac disease was completely neglected to a point where the Centers for Disease Control considers celiac disease a public health threat because it is unique in that so many are not diagnosed. With type 1 diabetes and multiple sclerosis, there is no way you will have symptoms and not be diagnosed. Not with celiac disease. Ninety-plus percent of the people with the disease are not diagnosed. They consume the health care system.

So now celiac disease is a topic of discussion at the National Institutes of Health, the Food and Drug Administration and CDC. It's remarkable. If you are new you might think it was always like this. All you know is you don't have to go to a special store for food. You can go to Safeway or Giant and find gluten-free products.

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AR: Is that what you were aiming for?

AF: Absolutely. Now my major aim is to change the name from celiac disease to celiac condition. I really don't want to have the word "disease" in there. When you go on a gluten-free diet and you have been diagnosed for some time, you don't have symptoms. You are indistinguishable from others. In that way it does not really affect your lifestyle other than the way you eat.

I speak with a new generation of chefs. They think gluten free is a challenge and they do not accept that the food cannot taste the same. Some make bread and it is indistinguishable from gluten-containing bread. My feeling is that we are on the verge of a major breakthrough here.

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We are moving away from the mom and pop operation. In the beginning, those who were making gluten-free products were the people who had celiac disease or had it in their family. The major players are now starting to come into the picture. The $1.7 billion gluten-free market now grows 20 percent per year.

AR: There is some fear the big players will knock out the mom and pop operations. Then if things calm down and some of the demand drops, the big companies will lose interest in the gluten-free market.

AF: If you do a market analysis right now and ask yourself how many people will buy gluten-free products, the answer is 60 million. Of course these are not all people with celiac disease. The number diagnosed with celiac disease is roughly 200,000. So you start to see two major categories. The ones who eat gluten-free for medical necessity who will never go away and the casual consumers who may come and go.

What's interesting is how big these two groups are. At our center, we did an analysis of almost 6,000 people. A small percent have wheat allergies, about .01 percent. Then the people who have celiac disease are one percent. What is astonishing is that the big part is the people who have gluten sensitivity. They make up six to seven percent of patients we see. Nationwide that is 20 million people and if they are sensitive to gluten, they will never go away.

AR: Does the improvement in the marketplace make people a little less interested in medical advances?

AF: I don't think so. The advanced knowledge that would give us an alternative way to handle the gluten-free diet—perhaps the pill—would give us peace of mind. I don't dispute that when you are at home, you control everything. The unknown is always when you are out of your control zone. Unfortunately, and this is mainly with the adult population, of those who follow the gluten-free diet and have no symptoms, 30 to 40 percent still have damaged intestines, meaning that they are not quite there yet.

There is still some minor cross-contamination that affects the complete healing of the intestine. We know that over time, this can be pricey health-wise. That is why it would be a really good thing to have something else, a safety net when you are not in your safety zone.

AR: You have proposed doing away with the biopsy as the gold standard for diagnosis of celiac disease. Where does that stand?

AF: We are getting there. If we had this discussion three months ago I would say the common denominator for celiac disease is pretty obvious. You are born with the genes, you eat gluten. The two key elements are there and that's when the autoimmune process starts. An aggressive immune system will put you over the edge right away and you will develop symptoms as a child. If you have a slow-paced immune system, it will materialize in symptoms in 20 to 30 years. That is the paradigm. We said the rule is genes plus gluten equal autoimmunity. Then we published a paper that threw this out of the window.

AR: The way it has always been presented you have to have the genes, you have to have the gluten but for some reason it kicks off in different people at different times. What in the study changed that explanation?

AF: The original design of the study was to take a big cohort and see how celiac disease develops over time so we can write the natural history of celiac disease. We thought we would be able to see the evolution of the silent celiac disease that was surfacing in clinical outcomes.

AR: So you would have expected some indication in the original blood test that the person had celiac disease all along?

AF: Yes. We thought if we study this cohort and see who is affected by celiac disease in 1974 we will follow them. The intention was just to follow the symptoms. (The study tested blood samples from about 3,500 people taken in 1974 and again in 1989.) But what we found instead was a steady increase in the number of people who were developing celiac disease, not just an increase in the number who were showing symptoms or showing an increase in the severity of the symptoms. We thought, "This is not possible." There was no way because that would imply that genes plus gluten is not enough, there has to be something else. We went back and revisited. The more we were looking at this, we realized this is real. Now we have a completely different paradigm.

We had people at 70 years old who did not have celiac disease and at 75 years old they had celiac disease. For 70 years, one lady was eating gluten and was not bothered then all of a sudden something put her over the edge and made her lose the capability to tolerate gluten. So the question is what is this something else?

AR: Do you have an answer to that question?

AF: It looks like is there is another variable and that is probably the composition of the bacteria that live within us.

A major achievement in science was we were able to sequence the human genome. We realized we are made by 30,000 genes per person. We are whatever we are because of the 30,000 genes. But how can you explain all the diseases you can have with only one genome? The only explanation is that we are the composition of two genomes. One is the human genome. It is the one we inherited from our mother and father. It will not change over time. If it is defective because of some genes that will make you at risk for celiac disease, we can't change it.

But there is a parallel genome called the microbiome made up of the genes of microorganisms that live in us. This microbiome can change all the time because we don't always have the same bacteria. They change from one person to another and change in the same individual all the time.

Let's say all of a sudden you get an infection, you take antibiotics, you have surgery, you have a pregnancy, which by the way are all examples in which your bacteria will change tremendously and are all linked to the unmasking of celiac disease. A lot of cases of celiac disease start after one of these occur. We always thought it was silent and was then unmasked for some reason by these things.

Let's say, indeed, that is not the case. What happened now, you have another microbiome, another set of genes from new bacteria, that switches from tolerance to gluten to the autoimmune process. That is the only way I can explain these results where people who, despite having the genes, did not have celiac disease (as determined by positive blood tests and other measures) until they were 60 years old.

AR: What does this mean to the average person who has celiac disease?

AF: Let's say hypothetically that I would be able to find out why those people who tolerated gluten for 60 years were protected from celiac disease. Let's say I find the composition of the microbiome that is effective so you would avoid having trouble with gluten. I could apply that information to make sure those at risk for celiac disease would keep that kind of composition so they would never lose tolerance—or I can delay it as much as possible. Now you can talk about prevention.

AR: What about eliminating the need for the biopsy to diagnose celiac disease?

AF: Confining the diagnosis to a rigid set of rules, which, by the way, I contributed to wrongly, does not reflect the real gluten world out there. We know there are clinical cases of celiac disease in which not all

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the criteria are there. We published a paper that said let's be a little more flexible. Let's set five major criteria and say you have to fulfill any four of the five:

One, you have to have symptoms we know are related to celiac disease—diarrhea, anemia, whatever.
Two, you have to have the autoantibodies we use for diagnosis— anti-tissue transglutaminase and antiendomysial antibodies.
Three, you have to have HLA-DQ2 and/or HLA-DQ8.
Four, the biopsy shows damage.
Five, your symptoms have to resolve when you go on a gluten free diet.

In this formula, if you have symptoms, the autoantibodies, the HLA genes and symptoms that go away, you can avoid the biopsy.

AR: What if you don't have the genes?

AF: Then you fulfill three of the five and it's not enough. If you don't have the genes, you have to have the biopsy. If the biopsy does not show the damage, then you don't fulfill the criteria.

AR: So the genes are no longer absolutely necessary?

AF: That's right. It's rare, but 2 to 3 percent of the people who are diagnosed with CD are HLA-DQ2/DQ8 negative. In these cases, the biopsy would be essential. It is obvious the vast majority of those who have celiac disease will fit all five criteria, but there are exceptions.

AR: You can imagine what a shift this is.

AF: Do you remember that we have always been in trouble in our center because we are always shifting paradigms? This started by saying, "Now look guys there is a lot of celiac disease in the United States, you did not see it." Then at the beginning we were pointed out as wrong. Do you think we are going to be in a different spot now or should we negate the evidence by saying, "Gee this will create a problem."

We can no longer call celiac disease a gluten sensitive enteropathy, which means the gold standard is the biopsy. To me it is not gold anymore. I don't know if it is even silver or bronze. I believe it is copper.

AR: How long do you think it will take until the idea of not always using the biopsy is accepted?

AF: It is going to take three stages. The first one we are in now, the "You must be out of your mind "stage. Second, people will say, "Well, let's take look at that." Third, they'll say, "I always said so." It will take a couple of years. I predict the new dialogue will say in selective cases the biopsy may not be necessary.

I was the one who said the gold standard was the biopsy. Now I am saying I was wrong. When we say the biopsy is the gold standard that means it has to be there. That is not really the best system. There is an array of possibilities. Perhaps in 90 out of 100 cases the biopsy is the gold standard but in 10 cases the biopsy is not clear cut.

AR: What are the problems with the biopsy?

AF: The biopsy is inconvenient and it comes with a cost to the health care system.

AR: Will there ever be a test that can diagnose celiac disease in patients who have already put themselves on a gluten-free diet?

AF: No. When people give up gluten, they don't give their physician the tools to identify which part of the spectrum they are on, meaning do they have celiac disease or are they gluten sensitive? One thing that is not changed, and will never change in my opinion, is that you need to understand which part of the spectrum you are in before you try the diet. You can't treat the disease before the diagnosis, in my humble opinion.

The interview was edited for space and clarity.
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More from Dr. Fasano on GF issues

In addition to topics covered in our main story, Alessio Fasano, MD, had interesting things to say about the following issues:

Amy Ratner: One of the possible treatments for celiac disease that has been discussed is a vaccine. What is the status of the development of a vaccine?

Alessio Fasano: It is still feasible, but it's a question of reeducating the immune system to act differently. It will take years, maybe up to 20 years to do that. Right now there is work on a sensitizing vaccine, for people who are already diagnosed. It is for those who have the HLA-DQ2 gene. The vaccine reprograms the immune system so you can tolerate gluten and eat normally. That is the idea.

AR: What can you tell us about the study into whether high-risk infants can be prevented from developing celiac disease by completely avoiding gluten for the first year?

AF: There are two schools of thought. One is if you delay the introduction of gluten, you just delay the onset of celiac disease. The other is maybe you give time to the immune system to mature and handle gluten better.

I would say if you give time for the immune system to mature and the microbiome to become the good one, you give the opportunity for gluten tolerance, if not for life, then for a long, long time.

Both schools of thought are based on retrospective evidence that has been published. We are now enrolling kids in a research study and will follow them over time and see what the real natural situation here is. Either you delay the introduction and you delay or prevent celiac disease, or it makes no difference

AR: What do you know about the FDA and the gluten-free definition?

AF: The FDA has been slowed down tremendously by people who had unrealistic expectations and who wanted the definition to be zero gluten. But the FDA has just finished the final draft document on the definition and will be posting it by the end of the year for public comment. After that they will finalize the definition.

AR: What about people who feel 20 ppm is not a safe level of gluten, only zero is safe?

AF: In biology, zero does not exist. You can make a zero-part-per-million product in a facility like NASA where you have special suits and then you will wind up with a slice of bread that will cost $2,000. But as soon as it comes out of the facility, it will be cross-contaminated by one or two parts of gluten.

The final study (on a safe level) is done and it is indisputably true. Of course we know there are people who are extremely sensitive, but you have to make the rules for the vast majority and I would say 20 ppm covers the vast majority.

AR: What do you think about the possibility that gluten-free grains are cross-contaminated?

AF: That is scary. This is the responsibility of the FDA, which isn't acting fast enough on deciding what gluten-free really is. General Mills decided to take one product that is naturally gluten free and market it by labeling it gluten free.

They did this right. They did everything they were supposed to to make sure it is not cross-contaminated. They put a big check "Gluten Free" and it is a blockbuster. But you have to do the homework.

As usual if the rules are not clear, people can cut corners. But when the FDA defines gluten free and attaches a legal consequence, trust me that will be deterrence by itself.

AR: Let's turn to gluten sensitivity, which has always been a kind of catchall term. Are there tests or other criteria that are being used now that allow for an official diagnosis?

AF: Gluten sensitivity was always disregarded by the medical and scientific community. If you come to my office and say I feel sick when exposed to gluten and I do my tests and I figure out you don't have celiac disease, I would say you don't have anything. There is no reason for you to be on a gluten free diet. These people got so desperate, they went to alternative medicine, chiropractic and other treatments. They tried special diets—gluten free, casein free, lactose free, whatever free.

These people mainly have behavior symptoms like a foggy mind, tingling fingers, joint pain, headaches, memory loss, hair loss and a wealth of others. There is still a sizable number of people who have the placebo effect, but there is definitely a group of others who are really and truly sensitive to gluten and when you remove gluten, they don't have symptoms.

The way we approach the story is: If you have symptoms related to gluten exposure, we look at where you fall in the spectrum. Do you have wheat allergy—no. Do you have celiac disease—no. Then by exclusion you are called gluten sensitive. We have papers coming out that start to give us some clues to some possible markers we can look at to make the diagnosis of gluten sensitivity.

AR: There are some questions and concerns about gluten sensitivity. How gluten free does someone who is gluten sensitive have to be? Do they always have to be gluten free? Can they base their gluten-free diet on whether they react to foods, as opposed to celiac disease where you have to avoid all gluten all the time?

AF: We get this question about gluten sensitivity all the time. When people come to the center, they say, "I have to be on the gluten-free diet so why do I care what I have?" Well there are tremendous differences there.

With one, celiac disease, you are going to have it for life. It is an autoimmune disease. It will not go away. You can't eat even a crumb. Your system will perceive it like you ate a whole loaf of bread. With gluten sensitivity, that's not necessarily so.

You may grow out of gluten sensitivity. Celiac disease has a genetic component so it can affect the rest of the family. Gluten sensitivity does not.

With celiac disease, if you make a mistake, not only do you pay the price on the spot because you get sick, but it contributes to comorbidities. With gluten sensitivity that is not necessarily so. If you make a mistake you pay the price, but nothing will happen to you over time. You definitely need to know where you fall on the spectrum. ■