

Celiac Disease: Unmasking an Elusive Enemy

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By Rita M. Rooney

Some observers might say Alessio Fasano, MD, came to this country looking for trouble. As a pediatric gastroenterologist, Fasano treated so many celiac patients in his native Italy that, when he moved to the U.S., he hoped to find a medical landscape where the disease, so prevalent in Europe, was less common. He didn't expect to learn, however, that celiac disease was virtually unknown among the medical community here, as well as by those living with its undiagnosed pain. At the time, the disease was estimated to affect no more than one in 10,000 people. It wasn't listed in the National Institutes of Health (NIH) annual directory of all diseases. In fact, it didn't even earn a mention among those conditions considered rare. So Fasano went looking for it, and indeed it turned out to be the trouble-maker he thought it was.

"This was very puzzling to me," says Fasano, professor of pediatrics, medicine, and physiology, and director of the University of Maryland Center for Celiac Research. "Everything we knew about celiac disease suggested that Americans should be as susceptible to it as Europeans. The genes are similar, and we all eat pasta and other wheat products."

Celiac is an auto-immune disease caused by a genetic predisposition, and by an environmental trigger, gluten, that is mismanaged by the body because of genetic makeup. A third factor is the presence of an intestinal leak, or the ineffective opening and closing of "doors" that help the intestine digest food. All three components—genes, gluten and intestinal leakage—are necessary for the onset of celiac disease. People suffering from the disease cannot eat anything containing wheat, rye or barley. Because the disease affects the small intestine, it manifests itself primarily as a gastrointestinal disorder, causing severe abdominal pain, chronic diarrhea or constipation, stomach distention and weight loss. However, any organ or tissue can be targeted. Children with the disease often suffer growth retardation, pubertal delay, iron deficiency anemia and bone loss. For celiac patients, pain is a constant companion and reminder that, if untreated, their condition can be life threatening—the consequence of malnutrition.

"When I saw that there were no celiac cases in this country, I realized there were two possibilities," Fasano says. "Either it was being overlooked, or there was a third factor preventing the disease-causing interaction between the genes and gluten. My curiosity got the best of me. I had to find out which."

A Search Begins

Curiosity is the driving force behind this former professional swimmer who dives head-first into questions previously untouched by science. In his early days at the university, he contributed an article to the *Journal of Gastroenterology*, asking, "Where Have All the American Celiacs Gone?" He then proceeded to find out.

"The scientific community was skeptical to be sure," he says. "There were polite and not-so-polite reactions to the premise that celiac disease might be a more serious problem than was thought. Generally, reactions boiled down to the suggestion that we were wasting our time. It didn't exist."

Under Fasano's guidance, the medical school's center for celiac research was born in 1996. "We soon realized the disease is not a problem that can be handled by a single discipline," he says. "Its complexity demands the collaboration of pediatricians, adult and pediatric gastroenterologists, epidemiologists, immunologists, geneticists, and molecular biologists."

He adds the center attracted top scientists with an intriguing proposition—the opportunity to study the only auto-immune disease for which the trigger was already known. "In science, you seek to minimize the unknowns," he says.

"In this case, we had the luxury of beginning with a critical known entity—the identity of the instigator." The prospect of investigating a disease in which the evolving research might be applied to other auto-immune conditions drew world-class scientists to the center, the first of its kind in the U.S. Epidemiologists were interested in discovering why the disease was prevalent in Europe but not in this country, although all the elements were similar. Molecular biologists wanted to know more about the signaling between gluten and the target cells. The mystery attached to celiac disease became a magnet for interdisciplinary scientific investigation, and so the center was created, founded on one goal—to improve the quality of life for celiac patients and their families.

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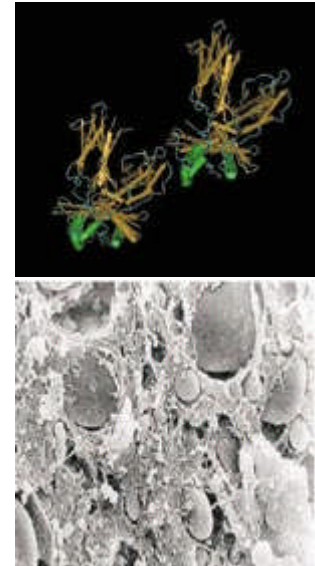
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Diagnosis - A First Step

One of the earliest problems the team encountered was the ineffectiveness of available diagnostic tools. Researchers in the Fasano laboratory developed an improvement on a test that had failed to discriminate between patients with an allergic reaction and those who had the auto-immune deficiency, as well as a later test that was specific but subject to human error. They developed an assay by cloning the human gene for anti-tissue transglutaminase (tTG), and coming up with an accurate and inexpensive, machine-operated test in which a drop of blood changes color to reveal specific antibodies. It is that diagnostic tool that is used routinely throughout the country today. A positive result must then be confirmed by an endoscopy with biopsy.

Until the advent of the tTG test, the NIH had been reluctant to fund large numbers of celiac studies because there was no reliable indication of prevalence, and no diagnostic tool to use for widespread screening. Using their new procedure, Fasano and his colleagues screened blood samples from 2,000 blood donors, and found the incidence to be, not one in 10,000 as originally thought, but one in 250. To the American scientific community, however, that study, though surprising, would have to be validated by endoscopic follow-up studies, proving the presence of celiac disease. So the team followed it with a study of 13,000 volunteers, some healthy individuals, and others who were symptomatic or had family members with classic celiac symptoms. That study, concluding that one in every 133 Americans has the disease, led to NIH support and assistance in communicating the devastating impact of celiac disease on American lives.



Crystallography (top) and a scan electron microscopy (bottom) of gluten, the protein that triggers celiac disease.

In 2004, largely prompted by papers published by Fasano and others, the NIH convened Consensus Development and State-of-the-Science Conferences on Celiac Disease. The process is the investigative method for evaluating scientific evidence on a given biomedical or public health issue, often for the purpose of resolving a controversy in clinical care. It is an exhaustive examination of fact and theory involving high-ranking objective scientists, as well as those working in a related field. Fasano was one of those addressing the conference, which concluded that celiac disease is “greatly underdiagnosed” and that it affects approximately three million Americans. That became the official position of the NIH, a position that continues to underscore the mission of Maryland’s center for celiac research in improving the lives of celiac sufferers. Frank A. Hamilton, MD, MPH, chief of the digestive diseases program, National Institute of Diabetes and Digestive and Kidney Diseases, NIH, worked with Fasano during the consensus conferences. He says, “Dr. Fasano’s tenacity in exploring the real prevalence of celiac disease, and his landmark 2003 paper, have changed medicine’s perception of a disease once considered rare and now known to be common. His work has provided seminal insight to what goes on in the intestines, and has been a catalyst in prompting many other investigators to study this disease.”

The Patient’s Plight

“For years, patients would come to us in desperation,” Fasano says. “Many had gone 15 years or more without a diagnosis. Doctors were forced to admit to patients there was nothing they could do for them. Some people were told their illness was psychosomatic. Some had lost hope, and had forgotten what it was not to be sick.”

He knew that, for every patient treated in the center’s clinic, there were hundreds still struggling to understand the source of their pain, and along with them, hundreds of clinicians who needed the conclusions of NIH-validated research to help guide their patients through the difficult hurdles of celiac disease. Commenting on the consensus findings of NIH, Fasano says that, after years of pushing a snowball uphill, the snowball was finally headed down a slippery slope. Even so, the only treatment available was a rigid gluten-free diet, not an easy course for anyone to follow.

“The diet has to be followed 100 percent,” Fasano says. “But for those who stick to it, there are rewards. A few months after beginning a gluten-free diet, a patient’s intestinal damage will be completely healed, and there will be no remaining evidence of celiac disease. But the diet is admittedly challenging. All processed foods contain glutes. They are present in sauces, beer, pizza, candies, ice cream, almost every food. For a celiac patient, eating in a restaurant is almost impossible. Even trying to explain one’s restrictions to a restaurant’s sympathetic chef is risky. A few drops of oil can set off a recurrence of symptoms.”

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Research and Discovery

While he started off with a goal of determining the prevalence of celiac disease in the U.S., and then to communicating an awareness to patients and the medical community, Fasano now turned his sights to additional research, aimed at the third factor in this baffling disease—intestinal leakage.

“We decided that, if we couldn’t remove the genes or the trigger, we would work on that third factor,” he says. “We discovered Zonulin, a protein that appears to be involved in many disease states in which leakage occurs in the tight junctions including the gastrointestinal tract. This led us to the belief that it might have an important role in the treatment of celiac disease.”

The center has since partnered with Alba Therapeutics, a University of Maryland School of Medicine start-up company located in the UMB Biopark facility, to develop an alternative treatment for the disease, based on the Zonulin discovery. The resulting therapy, for which the university retains intellectual property rights, is currently in Phase II trials, and Fasano is guardedly optimistic that a new treatment soon will be available, negating or reducing the need for a rigidly-controlled gluten-free diet.

For a man whose work allows few hours for relaxation, Fasano still finds time for swimming and tennis, and reports that, after turning 40, he took up two new leisure pursuits—motorcycles and the saxophone. Just mentioning the Harley-Davidson he bought recently prompts a somewhat wistful smile, as he talks about the rolling hills and farmland of Howard County to be explored on a sunny day.

“When I was young in Italy, a motorcycle was my primary means of transportation,” he says. “Then, for many years, I didn’t ride. So maybe this is a return to youth, or maybe an escape from highway traffic. Whatever it is, I really enjoy taking off on the Harley.”

Referring to the saxophone, he says being able to play for an hour or so in the evening is as relaxing as the Harley is sport. He likes to play accompanied by his son on the trombone. A strong investment in family is evidenced by pictures of his three children whose photos take up a prominent place in his office. He talks with pride of his oldest son who graduates from Embry Riddle Aeronautic University this year, and his nine-year-old, a member of an ice hockey traveling team, with whom he finds time to travel to out-of-town games. As for his daughter, Serena, a University of Maryland College Park freshman majoring in public health, he admits she may be the one to carry on the family tradition of medicine. “She worked here in the laboratory during summers, and she surprised even me by what she achieved,” he says.

It seems Serena, who was 14 at the time, decided that the good bacteria in yoghurt might have a scientific advantage. She added the yoghurt to specimen samples of E.coli in a Petri dish and found that it killed the E.coli. “I didn’t quite believe it at first,” Fasano says. “I made her repeat the experiment several times.”

Her first experiment stood the test of repetition and, like her father, Serena’s curiosity caused her to question why. She conducted two years of research and discovered that there is a protein in yoghurt that kills the E.coli. She has since earned a patent for her discovery, and hopes her work may someday lead to development of an antibiotic to cure patients with the deadly E.coli bacterial infection.

Success and Recognition

Research and efforts to alert the medical community to the realities of celiac disease have not dimmed Alessio Fasano’s intrinsic identity as healer. He still can be seen in the center’s clinic on a daily basis, treating patients, giving them the benefit of his optimism—an optimism born of his conviction that celiac disease was a presence that needed to be confronted head-on.

There have been impressive milestones in the relatively short life of the center for celiac research, not the least of which is the center’s role in spearheading the American Celiac Disease Alliance, resulting in a Congressional food labeling law that makes it easier for patients with the disease to identify safe food items. The center completed a case-finding study involving a network of 50 primary care physicians who enrolled more than 2,000 patients with celiac disease, underlining the center’s roadmap for increasing awareness by offering screening capabilities to physicians.

Advocacy for awareness was further corroborated in 2006 when the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition identified celiac disease as the disease of the year—this only a few years after it was considered practically non-existent in the U.S. Fasano’s personal honors have included Maryland’s Innovator of the Year Award, and the University of Maryland Baltimore 2006 Entrepreneur of the Year Award—all of which suggest that Fasano found the trouble he was looking for in the underdiagnosis of celiac disease. He found it—and he fixed it.