THE WAR ON

Wheat sensitivity isn't imaginary, most researchers now agree. But what's really behind it?

By **Kelly Servick**

The patients weren't crazy—Knut Lundin was sure of that. But their ailment was a mystery. They were convinced gluten was making them sick. Yet they didn't have celiac disease, an autoimmune reaction to that often-villainized tangle of proteins in wheat, barley, and rye. And they tested negative for a wheat allergy. They occupied a medical no man's land.

About a decade ago, gastroenterologists like Lundin, based at the University of Oslo, came across more and more of those enigmatic cases. "I worked with celiac disease and gluten for so many years," he says, "and then came this wave." Gluten-free choices began appearing on restaurant menus and creeping onto grocery store shelves. By 2014, in the United States alone, an estimated 3 million people without celiac disease had sworn off gluten. It was easy to assume that people claiming to be "gluten sensitive" had just been roped into a food fad.

"Generally, the reaction of the gastroenterologist [was] to say, 'You don't have celiac disease or wheat allergy. Goodbye,'" says Armin Alaedini, an immunologist at Columbia University. "A lot of people thought this is perhaps due to some other [food] sensitivity, or it's in people's heads."

PHOTO: PAUL TAYLOR/GETTY IMAGES

GLUTEN

Stretchy, resilient gluten allows bread to rise. But millions now shun it.

But a small community of researchers started searching for a link between wheat components and patients' symptoms—commonly abdominal pain, bloating, and diarrhea, and sometimes headaches, fatigue, rashes, and joint pain. That wheat really can make nonceliac patients sick is now widely accepted. But that's about as far as the agreement goes.

As data trickle in, entrenched camps have emerged. Some researchers are convinced that many patients have an immune reaction to gluten or another substance in wheat—a nebulous illness sometimes called nonceliac gluten sensitivity (NCGS).

Others believe most patients are actually reacting to an excess of poorly absorbed carbohydrates present in wheat and many other foods. Those carbohydrates—called FODMAPs, for fermentable oligosaccharides, disaccharides, monosaccharides, and polyols—can cause bloating when they ferment in the gut. If FODMAPs are the primary culprit, thousands of people may be on gluten-free diets with the support of their doctors and dietitians but without good reason.

Those competing theories were on display in a session on wheat sensitivity at a celiac disease symposium held at Columbia in March. In back-to-back talks, Lundin made the case for FODMAPs, and Alaedini for an immune reaction. But in an irony that underscores how muddled the field has become, both researchers started their quests believing something completely different.

KNOWN WHEAT-RELATED ILLNESSES have clear mechanisms and markers. People with celiac disease are genetically predisposed to launch a self-destructive immune response when a component of gluten called gliadin penetrates their intestinal lining and sets off inflammatory cells in the tissue below. People with a wheat allergy respond to wheat proteins by churning out a class of antibodies called immunoglobulin E that can set off vomiting, itching, and shortness of breath. The puzzle, for both doctors and researchers, is patients who lack both the telltale antibodies and the visible damage to their intestines but who feel real relief when they cut out gluten-containing food.

Some doctors have begun to approve and even recommend a gluten-free diet. "Ultimately, we're here not to do science, but to improve quality of life," says Alessio Fasano, a pediatric gastroenterologist at Massachusetts General Hospital in Boston who has studied NCGS and written a book on living gluten-free. "If I have to throw bones on the ground and look at the moon to make somebody better, even if I don't understand what that means, I'll do it."

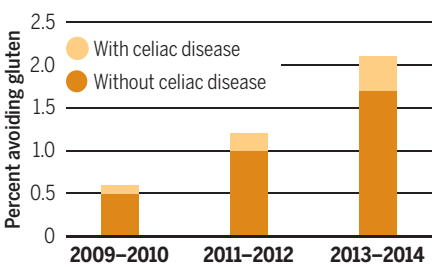
Like many doctors, Lundin believed that (fad dieters and superstitious eaters aside) some patients have a real wheat-related ailment. His group helped dispel the notion that NCGS was purely psychosomatic. They surveyed patients for unusual levels of psychological distress that might express itself as physical symptoms. But the surveys showed no differences between those patients and people with celiac disease, the team reported in 2012. As Lundin bluntly puts it: "We know they are not crazy."

Still, skeptics worried that the field had seized on gluten with shaky evidence that it was the culprit. After all, nobody eats gluten in isolation. "If we did not know about the specific role of gluten in celiac disease, we would never have thought gluten was responsible for [NCGS]," says Stefano Guandalini, a pediatric gastroenterologist at the University of Chicago Medical Center in Illinois. "Why blame gluten?"

Defenders of NCGS generally acknowledge that other components of wheat might contribute to symptoms. In 2012, a group of proteins in wheat, rye, and barley called amylase trypsin inhibitors emerged as a potential offender, for example, after a team led by biochemist Detlef Schuppan of Johannes Gutenberg University Mainz in Germany (then at Harvard Medical School in Boston) reported that those proteins can provoke immune cells.

Against the grain

Data from the National Health and Nutrition Examination Survey show the rising tide of gluten avoidance by people without celiac disease. Celiac diagnoses also rose, but probably not its actual prevalence.



But without biological markers to identify people with NCGS, researchers have relied on self-reported symptoms measured through a "gluten challenge": Patients rate how they feel before and after cutting out gluten. Then doctors reintroduce gluten or a placebo—ideally disguised in indistinguishable pills or snacks—to see whether the symptoms tick back up.

Alaedini has recently hit on a more objective set of possible biological markers—much to his own surprise. "I entered this completely as a skeptic," he says. Over his career, he has gravitated toward studying spectrum disorders, in which diverse symptoms have yet to be united under a clear biological cause—and where public misinformation abounds. His team published a study in 2013, for example, that debunked the popular suggestion that children with autism had high rates of Lyme disease. "I do studies [where] there is a void," he says.

In NCGS, Alaedini saw another poorly defined spectrum disorder. He did accept that patients without celiac disease might somehow be sensitive to wheat, on the basis of several trials that measured symptoms after a blinded challenge. But he was not convinced by previous studies claiming that NCGS patients were more likely than other people to have certain antibodies to gliadin. Many of those studies lacked a healthy control group, he says, and relied on commercial antibody kits that gave murky and inconsistent readings.

In 2012, he contacted researchers at the University of Bologna in Italy to obtain blood samples from 80 patients their team had identified as gluten sensitive on the basis of a gluten challenge. He wanted to test the samples for signs of a unique immune response—a set of signaling molecules different from those in the blood of healthy volunteers and celiac patients. He wasn't optimistic. "I thought if we were going to see something, like with a lot of spectrum conditions that I have looked at, we would see small differences."

The results shocked him. Compared with both healthy people and those with celiac, these patients had significantly higher levels of a certain class of antibodies against gluten that suggest a short-lived, systemic immune response. That didn't mean gluten itself was causing disease, but the finding hinted that the barrier of those patients' intestines might be defective, allowing partially digested gluten to get out of the gut and interact with immune cells in the blood. Other elements—such as immune response–provoking bacteria—also might be escaping. Sure enough, the team found elevated levels of two proteins that indicate an inflammatory response to bacteria. And when 20 of the same patients spent 6 months on a gluten-free diet, their blood levels of those markers declined.

For Alaedini, the beginnings of a mechanism emerged: Some still-unidentified wheat component prompts the intestinal lining to become more permeable. (An imbalance in gut microbes might be a predisposing factor.) Components of bacteria then seem to sneak past immune cells in the underlying intestinal tissue and make their way to the bloodstream and liver, prompting inflammation.

GRAPH: J. YOU/SCIENCE

"This is a real condition, and there can be objective, biological markers for it," Alaedini says. "That study changed a lot of minds, including my own."

The study also impressed Guandalini, a longtime skeptic about the role of gluten. It "opens the way to finally reach an identifiable marker for this condition," he says.

BUT OTHERS SEE the immune-response explanation as a red herring. To them, the primary villain is FODMAPs. The term, coined by gastroenterologist Peter Gibson at Monash University in Melbourne, Australia, and his team, encompasses a smorgasbord of common foods. Onions and garlic; legumes; milk and yogurt; and fruits including apples, cherries, and mangoes are all high in FODMAPs. So is wheat: Carbs in wheat called fructans can account for as much as half of a person's FODMAP intake, dietitians in Gibson's group have estimated. The team found that those compounds ferment in the gut to cause symptoms of irritable bowel syndrome, such as abdominal pain, bloating, and gas.

Gibson has long been skeptical of studies implicating gluten in such symptoms, arguing that those findings are hopelessly clouded by the nocebo effect, in which the mere expectation of swallowing the dreaded ingredient worsens symptoms. His team found that most patients couldn't reliably distinguish pure gluten from a placebo in a blinded test. He believes that many people feel better after eliminating wheat not because they have calmed some intricate immune reaction, but because they've reduced their intake of FODMAPs.

Lundin, who was firmly in the immune-reaction camp, didn't believe that FODMAPs could explain away all his patients. "I wanted to show that Peter was wrong," he says. During a 2-week sabbatical in the Monash lab, he found some quinoa-based snack bars designed to disguise the taste and texture of ingredients. "I said, 'We're going to take those muesli bars and we're going to do the perfect study.'"

His team recruited 59 people on self-instituted gluten-free diets and randomized them to receive one of three indistinguishable snack bars, containing isolated gluten, isolated FODMAP (fructan), or neither. After eating one type of bar daily for a week, they reported any symptoms. Then they waited for symptoms to resolve and started on a different bar until they had tested all three.

Before analyzing patient responses, Lundin was confident that gluten would cause the worst symptoms. But when the study's blind was lifted, only the FODMAP symptoms even cleared the bar for statistical significance. Twenty-four of the 59 patients had their highest symptom scores after a week of the fructan-laced bars. Twenty-two responded most to the placebo, and just 13 to gluten, Lundin and his collaborators—who included Gibson—reported last November in the journal *Gastroenterology*. Lundin now believes FODMAPs explain the symptoms in most wheat-avoiding patients. "My main reason for doing that study was to find out a good method of finding gluten-sensitive individuals," he says. "And there were none. And that was quite amazing."

AT THE COLUMBIA MEETING, Alaedini and Lundin went head to head in consecutive talks titled "It's the Wheat" and "It's FODMAPS." Each has a list of criticisms of the other's study. Alaedini contends that by recruiting broadly from the gluten-free population, instead of finding patients who reacted to wheat in a challenge, Lundin likely failed to include people with a true wheat sensitivity. Very few of Lundin's subjects reported symptoms outside the intestines, such as rash or fatigue, that might point to a widespread immune condition, Alaedini says. And he notes that the increase in patients' symptoms in response to the FODMAP snacks was just barely statistically significant.

Lundin, meanwhile, points out that the patients in Alaedini's study didn't go through a blinded challenge to check whether the immune markers he identified really spiked in response to wheat or gluten. The markers may not be specific to people with a wheat sensitivity, Lundin says.

Despite the adversarial titles of their talks, the two researchers find a lot of common ground. Alaedini agrees that FODMAPs explain some of the wheat-avoidance phenomenon. And Lundin acknowledges that some small population may really have an immune reaction to gluten or another component of wheat, though he sees no good way to find them.

After the meeting, Elena Verdú, a gastroenterologist at McMaster University in Hamilton, Canada, puzzled over the polarization of the field. "I don't understand why there is this need to be so dogmatic about 'it is this, it is not that,'" she says.

She worries that the scientific confusion breeds skepticism toward people who avoid gluten for medical reasons. When she dines with celiac patients, she says, waiters sometimes meet requests for gluten-free food with smirks and questions. Meanwhile, the conflicting messages may send nonceliac patients down a food-avoidance rabbit hole. "Patients are withdrawing gluten first, then lactose, and then FODMAPs—and then they are on a really, really poor diet," she says.

But Verdú believes careful research will ultimately break through the superstitions. She is president of the North American Society for the Study of Celiac Disease, which this year awarded its first grant to study nonceliac wheat sensitivity. She's hopeful that the search for biomarkers like those Alaedini has proposed will show that inside the monolith of gluten avoidance lurk multiple, nuanced conditions. "It will be difficult," she says, "but we are getting closer." ■

Although consumers focus on gluten, other wheat components could be at the root of symptoms.

PHOTO: MATT RAINEY/THE NEW YORK TIMES

The war on gluten

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