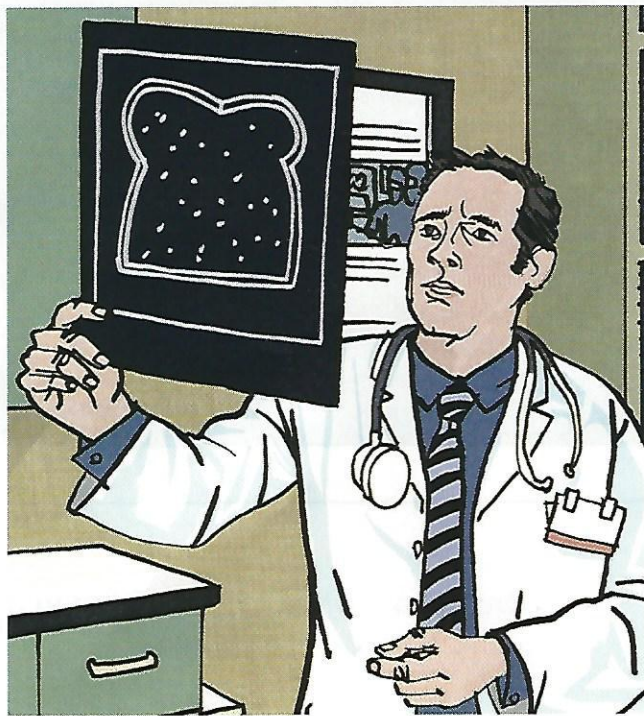


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# The Trouble with Gluten

Gluten may not be the only wheat protein that can make people sick



Two years ago, at the recommendation of a nutritionist, I stopped eating wheat and a few other grains. Within a matter of days the disabling headaches and fatigue that I had been suffering for months vanished. Initially my gastroenterologist interpreted this resolution of my symptoms as a sign that I perhaps suffered from celiac disease, a peculiar disorder in which the immune system attacks a bundle of proteins found in wheat, barley and rye that are collectively referred to as gluten. The misdirected assault ravages and inflames the small intestine, interfering with the absorption of vital nutrients and thereby causing bloating, diarrhea, headaches, tiredness and, in rare cases, death. Yet several tests for celiac disease had come back negative. Rather my doctors concluded that I had nonceliac “gluten sensitivity,” a relatively new diagnosis. The prevalence of gluten sensitivity is not yet clear, but some data suggest it may afflict as many as 6 percent of Americans, six times the number of people with celiac disease.

Although gluten sensitivity and celiac disease share many symptoms, the former is generally less severe. Compared with individuals with celiac disease, people with gluten sensitivity are more likely to report nondigestive symptoms such as headaches and do not usually suffer acute intestinal damage and inflamma-

tion. Lately, however, some researchers are wondering if they were too quick to pin all the blame for these problems on gluten. A handful of new studies suggest that in many cases gluten sensitivity might not be about gluten at all. Rather it may be a misnomer for a range of different illnesses triggered by distinct molecules in wheat and other grains.

“You know the story of the blind man and the elephant? Well, that’s what gluten-sensitivity research is right now,” says Sheila Crowe, head of research at the gastroenterology division at the School of Medicine at the University of California, San Diego. As doctors continue to tease apart the diverse ways that the human body reacts to all the proteins and other molecules besides gluten that are found in grains, they will be able to develop more accurate tests for various sensitivities to those compounds. Ultimately clinicians hope such tests will help people who have a genuine medical condition to avoid the specific constituents of grains that make them ill and will stop others from unnecessarily cutting out nutrient-dense whole grains.

## SEEDS OF SICKNESS

AMONG THE MOST COMMONLY CONSUMED GRAINS, wheat is the chief troublemaker. Humans first domesticated the wheat plant about 10,000 years ago in the Fertile Crescent in the Middle East. Since then, the amount of wheat in our diet—along with all the molecules it contains—has dramatically increased. Of all these molecules, gluten is arguably the most important to the quality of bread because it gives baked goods their structure, texture and elasticity. When bakers add water to wheat flour and begin to knead it into dough, two smaller proteins—gliadin and glutenin—change shape and bind to each other, forming long, elastic loops of what we call gluten. The more gluten in the flour, the more the dough will stretch and the spongier it will be once baked.

Until the Middle Ages, the types of grain that people cultivated contained far smaller amounts of gluten than the crops we grow today. In the following centuries—even before people understood what gluten was—they selectively bred varieties of wheat that produced bread that was lighter and chewier, inexorably increasing consumption of the protein. As technology for breeding and farming wheat improved, Americans began to produce and eat more wheat overall. Today the average person in the U.S. eats around 132 pounds of wheat a year—often in the form of bread, cereal, crackers, pasta, cookies and cakes—which translates to about 0.8 ounce of gluten each day.

Although historical records dating from the first century A.D. mention a disorder that sounds a lot like celiac disease, it was not until the mid-1900s that doctors realized the gluten in wheat



was to blame. During World War II, Dutch physician Willem-Karel Dicke documented a sharp drop in the number of deaths among children with the severest forms of celiac disease in parallel with a bread shortage. In a follow-up study, researchers removed different components of wheat from the diet of 10 children with the intestinal illness. Adding back gluten caused symptoms such as diarrhea to resurface, but reintroducing a different complex molecule found in wheat, namely starch, did not. Thus, gluten was shown to be responsible for celiac disease.

Later experiments by other researchers revealed which component of gluten provokes the immune system. When digested, gluten splits back into gliadin and glutenin. For reasons that remain unclear, the immune system of people with celiac disease treats gliadin in particular as though it were a dangerous invader.

For years doctors used diet to diagnose the gut disorder: if someone's symptoms disappeared on a gluten-free diet, then that person had celiac disease. Over time, however, clinicians developed more sophisticated ways to identify celiac disease, such as tests that look for immune system molecules known as antibodies that recognize and cling to gliadin. With the advent of such tests, clinicians soon discovered that some people who became mildly ill after eating bread and pasta did not in fact have celiac disease: biopsies revealed little or no intestinal damage, and blood tests failed to find the same antibodies associated with the disorder. In the process, the new condition became known as nonceliac gluten sensitivity.

Now several studies hint that so-called gluten sensitivity might not always be caused by gluten. In some cases, the problem may be entirely different proteins—or even some carbohydrates. “We’re so used to dealing with gluten as the enemy, but it might actually be something else,” says David Sanders, who teaches gastroenterology at the University of Sheffield in England. Joseph Murray, a gastroenterologist at the Mayo Clinic in Rochester, Minn., agrees: “I’m starting to feel more uncomfortable calling it nonceliac gluten sensitivity. I think it might be better to call it nonceliac wheat sensitivity.”

### AGAINST THE GRAIN

IF THE CULPRITS BEHIND CERTAIN INSTANCES of gluten sensitivity are, in fact, wheat constituents other than gluten, finding the right ones will be difficult. Wheat has six sets of chromosomes and a whopping 95,000 or so genes. In comparison, we humans have just two sets of chromosomes and about 20,000 genes. Genes code the instructions to build proteins, so more genes mean more proteins to sift through. Some initial experiments have spotlighted a few potential offenders, however.

In laboratory tests, wheat proteins known as amylase-trypsin inhibitors have stimulated immune cells in plastic wells to release inflammatory molecules called cytokines that can overexcite the immune system. Further tests showed that these wheat proteins provoked the same inflammatory response in mice. Likewise, in an Italian study, small concentrations of wheat germ agglutinin, a protein distinct from gluten, roused cytokines from human intestinal cells growing in a plastic well.

Preliminary research suggests that, in other cases, by-products of gluten digestion may be the problem. Breaking down gli-

adin and glutenin produces even shorter chains of amino acids—the building blocks of proteins—some of which may behave like morphine and other soporific opiates. Perhaps these molecules explain some of the lethargy exhibited by people who do not have celiac disease but are nonetheless sensitive to wheat, suggests Aristo Vojdani, chief executive officer of Immunosciences Lab in Los Angeles. In a small study by Vojdani and his colleagues, the blood of people classified as gluten-sensitive had higher levels of antibodies that recognize these gluten by-products than blood taken from healthy volunteers.

A final group of potential culprits belongs to a diverse family of carbohydrates such as fructans that are notorious for being difficult to digest. A failure to absorb these compounds into the blood may draw excess water into the digestive tract and agitate its resident bacteria. Because these resilient carbohydrates occur in all kinds of food—not just grains—a gluten-free or wheat-free diet will not necessarily solve anything if these molecules truly are to blame.

### NO PIECE OF CAKE

DESPITE THE RECENT EVIDENCE that wheat sensitivities are more numerous and varied than previously realized, research has also revealed that many people who think they have such reactions do not. In a 2010 study, only 12 of 32 individuals who said they felt better on a diet that excluded gluten or other wheat proteins actually had an adverse reaction to those molecules. “Thus, about 60 percent of the patients underwent an elimination diet without any real reason,” notes study author Antonio Carroccio of the University of Palermo in Italy.

Nevertheless, uncovering nongluten agitators of illness will give doctors a more precise way to diagnose grain sensitivities and help people avoid certain foods. Researchers could, for example, design blood tests to look for antibodies that bind to various short chains of amino acids or proteins such as wheat germ agglutinin, explains Umberto Volta, a gastroenterologist at the University of Bologna in Italy. And some scientists think ongoing research will eventually yield new therapies. “If we know what triggers the immune system, we hope we can switch the system off and cure the disease,” says Roberto Chignola of the University of Verona in Italy.

Personally, I suspect that something besides gluten might trigger my own symptoms. On occasion, I have tried gluten-free grain-based products such as beer made from barley from which the gluten has been extracted. Every time my headaches came roaring back with a vengeance (far sooner than any hangover might have struck), making me all the more suspicious that gluten is not the root of my troubles.

If that is true, and there is even the remote possibility of safely reinstating gluten in my diet, I would really like to know. As a New Yorker, it is hard for me to forgo pizza. If gluten was vindicated in my case, perhaps I could add it to nongrain flours or otherwise cook up experimental pizza at home and get those gooey, stretchy slices out of my dreams and onto my plate. ■

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