Chris Kresser
LET'S TAKE BACK YOUR HEALTH—*Starting Now.*

EBOOK

Should You Go Gluten-Free?

by CHRIS KRESSER

Should You Go Gluten-Free?

The Science Behind Non-Celiac Gluten Intolerance

Celiac disease (CD) was initially described in the first century A.D. by a Greek physician named Aretaeus of Cappadocia. (1) But neither Aretaeus nor anyone else knew that CD is caused by an autoimmune reaction to gluten, a protein in wheat. That didn't become clear until 1950 — several centuries later — when Dr. Willem Dicke, a Dutch pediatrician, conclusively proved that gluten was the culprit. (2) Dicke's discovery saved millions of children and adults from the perils of untreated celiac disease, including malnutrition, stunted growth, cancer, severe neurological and psychiatric illness, and even death.

Since then, the mainstream view of gluten intolerance has been relatively black or white: Either you have celiac disease, in which case even a small amount of gluten will send you running to the bathroom in three seconds flat, or you don't, and you can chug down beer and bagels without fear. However, it's becoming more and more clear that celiac disease is only one manifestation of gluten intolerance, and that "non-celiac gluten sensitivity" (i.e. people that react to gluten but do not have celiac disease) is a legitimate health condition.

Even so, the media has downplayed the significance of non-celiac gluten sensitivity (NCGS), even going as far as to suggest that it doesn't exist. This "all-or-nothing" view has led to some doctors telling patients that suspect they're sensitive to gluten but test negative for CD that they're simply imagining an affliction that doesn't exist.

It turns out those doctors are wrong. A growing body of evidence proves that NCGS is not only real, but is potentially a much larger problem than celiac disease.

50 Shades of Gluten (Intolerance)

To help you understand how a person can be gluten intolerant without having celiac disease, I need to give you a quick lesson in the biochemistry of wheat and wheat digestion.

Wheat contains several different classes of proteins. Gliadins and glutenins are the two main components of the gluten fraction of the wheat seed. (They're essential for giving bread the ability to rise properly during baking.) Within the gliadin class, there are four different epitopes (i.e. types): alpha-, beta-, gamma- and omega-gliadin. Wheat also contains agglutinins (proteins that bind to sugar) and prodynorphins (proteins involved with cellular communication). Once wheat is consumed, enzymes in the digestive tract called tissue transglutaminases (tTG) break down the wheat compound. In this process, additional proteins are formed, including deamidated gliadin and gliadorphins (aka gluteomorphins).

Here's the crucial thing to understand: Celiac disease is characterized by an immune response to a specific epitope of gliadin (alpha-gliadin) and a specific type of transglutaminase (tTG-2). But we now know that people can (and do) react to several other components of wheat and gluten — including other epitopes of gliadin (beta, gamma, omega), glutenin, WGA and deamidated gliadin — as well as other types of transglutaminase, including type 3 (primarily found in the skin) and type 6 (primarily found in the brain). (3, 4, 5, 6, 7, 8)

This is a huge problem because conventional lab testing for CD and gluten intolerance only screens for antibodies to alpha-gliadin and transglutaminase-2. If you're reacting to any other fractions of the wheat protein (e.g., beta-gliadin, gamma-gliadin or omega-gliadin), or any other types of transglutaminase (e.g., type 3 or type 6), you'll test negative for CD and gluten intolerance no matter how severely you're reacting to wheat.

BEYOND CELIAC: WHY CD IS JUST THE TIP OF THE ICEBERG

Official statistics suggest that Celiac disease affects between 0.7 percent and 1 percent of the U.S. population. (9) But considering the limited scope of the testing, it's possible that the actual incidence might be much higher.

But CD is only the tip of the iceberg when it comes to gluten intolerance. Celiac disease is caused by a distinct autoimmune response to wheat proteins and transglutaminase

enzymes in the gut. And as we've seen, this is just one possible expression of gluten intolerance; there are many other ways that sensitivity to gluten can manifest in the body. These are collectively referred to as "non-celiac gluten sensitivity," or NCGS.

There's no consensus definition of NCGS yet, but the most common understanding is that it's a reaction to gluten that is not autoimmune (like CD) or allergic (like wheat allergy). Another definition I've seen is, "a reaction to gluten that resolves when gluten is removed from the diet and CD and allergy have been ruled out." (10)

WHY GLUTEN INTOLERANCE IS LIKELY MORE COMMON THAN CURRENTLY ESTIMATED

Estimates for the prevalence of NCGS vary widely, ranging from 0.5% on the low end to 13% or higher on the high end. (11) However, there are several reasons why I believe NCGS is much more common than currently estimated.

First off, it's difficult to estimate the prevalence of NCGS because there is no definitive diagnostic test for it. As I mentioned above, the currently available tests for gluten sensitivity are primitive and only screen for a small fraction of the components of wheat that people react to. Further, even the best serological (blood) testing is not 100 percent accurate. An elimination/provocation challenge, where gluten is removed from the diet for 60–90 days, and then reintroduced, is still the gold standard for diagnosing gluten intolerance. However, many physicians are unaware of this and thus do not suggest it to their patients.

Another issue is the variety of symptoms caused by CD and NCGS. While most people assume that gluten intolerance always causes digestive distress, this is not the case. Many physicians and patients only suspect—and therefore test for—gluten intolerance when digestive symptoms are present. However, both gluten intolerance and celiac disease can present without any gut symptoms, and only extra-intestinal symptoms like ataxia, schizophrenia, dermatitis, or neuropathy. In fact, **the majority of patients** with neurological manifestations of gluten sensitivity have no gastrointestinal symptoms! (12)

In the case of celiac disease, which has been better studied than NCGS so far, about 30 percent of newly diagnosed patients do not have gut symptoms, and for every new case that is diagnosed, there are 6.4 cases that are undiagnosed—the majority of which are atypical or "silent" forms without gut symptoms. (13, 14)

Gluten intolerance can affect nearly every tissue in the body, including the brain, skin, endocrine system, stomach, liver, blood vessels, smooth muscles, and even the nuclei of cells. CD and NCGS are associated with an astonishing variety of diseases, including schizophrenia, epilepsy, Type 1 diabetes, osteoporosis, dermatitis, psoriasis, Hashimoto's hypothyroidism, and peripheral neuropathy. (15) Because the range of symptoms associated with gluten intolerance is so broad and nonspecific (i.e. can be attributed to any number of conditions), many patients and doctors don't suspect gluten may be the cause.

Even with these limitations, some researchers have speculated that NCGS may affect as many as 1 in 10 people. (16) I suspect this is accurate, if not conservative.

When Gluten-Free Is Not a Fad

Despite the rapidly-accumulating body of evidence supporting the existence of non-celiac gluten sensitivity, some mainstream medical professionals continue to insist that NCGS doesn't exist. To make things worse, a glut of stories in the popular media also suggest that non-celiac gluten sensitivity is a myth:

- **Science Proves Gluten Sensitivity Isn't Real, People Are Just Whiners**
- **The Science Is In — Why Gluten Sensitivity Is Probably Fake**
- **Gluten Intolerance May Be Completely Fake: Study**
- **Non-Celiac Gluten Sensitivity May Not Exist**
- **Gluten Intolerance May Not Exist**

Even late-night TV host Jimmy Kimmel **weighed in with a segment** that got a lot of attention in both popular and social media.

What strikes me about those stories—aside from how embarrassing they are as examples of so-called "science journalism"—is how eager the general public seems to be to prove that gluten intolerance is an imaginary or fake condition. I'm not exactly sure why this is. Maybe it's because gluten-containing foods and beverages like bread and beer have played such a central role in our culture for thousands of years. Or perhaps people simply distrust anything they perceive to be inauthentic or "faddish."

While I can relate to an aversion to fads (don't get me started on hipsters), and the gluten-free diet could in some ways be described as a fad, the consensus in the

scientific literature is that non-celiac gluten sensitivity is a bona-fide condition with numerous—and potentially serious—manifestations.

IS REMOVING GLUTEN FROM YOUR DIET DANGEROUS?

A common objection to gluten-free diets that we often hear from conventional dietitians and physicians is that they are somehow unsafe or dangerous. This is presumably because foods that contain gluten contain some magic ingredient that humans cannot live without.

The most glaring problem with this argument is the simple fact that humans have only been consuming gluten for the past 11,000 years or so, which represents a tiny fraction of our evolutionary history. That's about 367 generations, compared to the 66,000 generations we evolved in an environment without gluten or cereal grains.

The second problem with this argument is that even whole grains are not very nutrient dense. In fact, when compared with other foods like organ meats, fish, meats, vegetables, and fruits, whole grains are at the bottom of the list. (17) As you'd suspect, refined grains (like flour) are even lower. This is significant because 85 percent of the grain consumed in the US is in the highly refined form, and refined flour accounts for approximately 20 percent of calories consumed by the average American. (18)

Finally, studies that have assessed the nutritional quality of gluten-free diets have, not surprisingly, found that they are not lacking in any necessary nutrient. (19) If anything, people on a gluten-free diet are more likely to increase their intake of essential nutrients, especially if they replace breads and other flour products with whole foods (rather than with gluten-free flour alternatives).

WHAT THE SCIENCE REALLY SAYS ABOUT GLUTEN INTOLERANCE

According to a review paper called "Non-Celiac Gluten Sensitivity: The New Frontier of Gluten Related Disorders":

"…a rapidly increasing number of papers have been published by many independent groups, confirming that GS [non-celiac gluten sensitivity] should be included in the spectrum of gluten-related disorders." (20)

As I mentioned earlier, observational studies have linked gluten intolerance with a shockingly diverse range of symptoms and conditions, including:

- Irritable bowel syndrome (21)
- Fibromyalgia (22)
- Dermatitis and other skin conditions (23)
- Multiple sclerosis (24)
- Peripheral neuropathy, myopathy, and other neurological disorders (25)
- Schizophrenia (26)
- Depression (27)
- Attention deficit hyperactivity disorder (28)
- Ataxia (29)
- Type 1 diabetes (30)
- Autism spectrum disorders (31)
- Ménière disease (32)
- Endometriosis (33)
- Insulin resistance and inflammation (34)

I could go on, but I think you get the point. If the authors of the "gluten intolerance is fake" articles had spent even five minutes examining the research, they would have seen numerous papers supporting the existence of non-celiac gluten sensitivity.

And they aren't just observational studies; some of them are randomized clinical trials (RCTs), which are considered to be the gold standard of medical evidence. I'll describe one of these double-blind, placebo-controlled trials below, this one with the additional benefit of a crossover design. (35)

The researchers enrolled 61 participants without celiac disease or wheat allergy, but with self-identified gluten intolerance. Subjects were then randomly assigned to two groups; one was given a capsule with 4.4 grams per day of gluten (roughly the amount in two slices of white bread), and the other was given a placebo capsule containing only rice starch. After one week of a gluten-free diet, participants then "crossed over" into the other group (those that received the gluten capsules during the first round got rice starch, and vice versa). Crossover studies are advantageous because each crossover participant serves as his or her own control, which reduces the likelihood of confounding variables influencing the results.

The researchers found that intake of gluten significantly increased symptoms—both intestinal symptoms like bloating and abdominal pain, and extra-intestinal symptoms like depression, brain fog, and canker sores—compared to placebo.

As you can see, despite the rash and uninformed claims you may have seen in the popular media, gluten intolerance is indeed a real condition and not just a figment of the imagination. (Of course, if you happen to be one of the people that suffers from gluten intolerance, you didn't need me—or any study—to tell you that!)

It's disheartening to see so many sensational and poorly researched news stories making the claim that gluten intolerance is not a legitimate condition. Not only were those authors wrong, they were irresponsible and failed to do even the most basic background research about the subject they were writing about. This should be yet another reminder to take what you read in the popular health media with a large grain of salt.

Gluten Sensitivity vs. Wheat Sensitivity

One study that was cited frequently in the media as "proof" that gluten sensitivity doesn't exist found that a group of patients with irritable bowel syndrome (IBS) were not sensitive to gluten. (36) The researchers who performed this study had previously published a paper showing that IBS patients were sensitive to wheat, and that removing wheat from their diet led to an improvement of symptoms.

However, in this new study, the authors specifically isolated gluten and found that there was no difference in symptoms between the patients eating high-gluten diets and those eating low-gluten diets.

This is a significant finding, but to claim that it proves that non-celiac gluten sensitivity doesn't exist is both inaccurate and irresponsible. It's a great way to get clicks and generate attention, but it's an extreme distortion of what the study actually found.

WHY THIS STUDY DOESN'T DISPROVE GLUTEN SENSITIVITY

First, this study examined the effects of gluten in a specific population: people with irritable bowel syndrome. Even if it is true that gluten sensitivity is no more common in people with IBS than in people without IBS (which is premature to conclude on the basis

of a single study), it does not overturn the large body of evidence that links non-celiac gluten sensitivity to a variety of health problems. (37, 38, 39, 40)

Second, this study does not suggest that people with IBS—or anyone else with gluten sensitivity—should feel free to start chowing down on wheat. In fact, it suggests the opposite. For the first week of the trial, all patients were put on a gluten-free diet that was also low in FODMAPs (a class of carbohydrates present in wheat, as well as other foods).

After this lead-in period, the participants were assigned to one of three groups: a high-gluten diet, a low-gluten diet, and a placebo. Those on the high gluten diet were given 16 grams per day of purified wheat gluten; those on the low gluten diet were given 2 grams per day of purified wheat gluten plus 14 grams per day of whey protein isolate; and those on the placebo diet were given 16 grams per day of whey protein isolate.

The majority of participants experienced a significant improvement of symptoms during the 7-day gluten-free, low FODMAP lead-in period. But there was no difference in symptoms between the high gluten, low gluten, or placebo groups during the subsequent treatment period. In other words, patients did react adversely to wheat, but they did not react to isolated gluten.

This of course suggests that something other than gluten in the wheat was causing the problems patients experienced. As previously mentioned, we now know that there are several compounds in wheat other than gluten that could be to blame. These include not only FODMAPs, but also the aforementioned agglutinins, prodynorphins, deamidated gliadin, and gliadorphins. (41)

Another possibility is that both the placebo and low-gluten groups were reacting to the whey protein. Whey is >99% casein- and lactose-free, which is what most people who are sensitive to dairy react to. However, it is certainly possible for people to react adversely to whey, and in my experience this is more common with patients with digestive problems. If some of the “placebo” and low-gluten patients were, in fact, sensitive to whey, then that would invalidate the results of the study.

IS “NON-CELIAC WHEAT SENSITIVITY” A BETTER LABEL?

This study showed that for people with IBS on a low FODMAP diet, eating isolated gluten does not cause symptoms. But one might ask: who cares? Do you eat isolated,

purified gluten? Do you know anyone who does? I doubt it. People eat wheat—not gluten. And as both this study and numerous other studies have demonstrated, there are several components of wheat other than gluten that cause problems.

If there's an important takeaway from this study, it's this: non-celiac wheat sensitivity may be a different clinical entity than non-celiac gluten sensitivity. The former would be used to describe patients that are intolerant of wheat, but are able to eat other gluten-containing foods without symptoms. The latter would apply to patients who are sensitive to any food or product that contains gluten, including wheat. In fact, this distinction was originally proposed by researchers in response to another study which found no effects of gluten in patients on a low FODMAP diet. (42)

HOW TO FIND OUT IF YOU'RE SENSITIVE TO WHEAT, GLUTEN, OR BOTH

In practical terms, this study still supports the idea that patients with IBS should avoid wheat, because it contains FODMAPs and possibly other compounds that make them feel worse. What this study does tell us is that it's possible that IBS patients may be able to tolerate other non-wheat products that contain gluten, presuming they are low in FODMAPs and other compounds that they may react to.

Here's the best way to determine if this is true for you:

1. Remove all gluten-containing foods and products from your diet for 60 days.
2. At the end of the 60 day period, cook up a bowl of barley, eat it, and see what happens.
3. A few days later, eat a piece of wheat bread.

Barley is a gluten-containing grain that is low in FODMAPs. If you react to it, that suggests you're intolerant of gluten or other gluten-like compounds. If you don't react to barley, but you do react to the wheat bread, that suggests you are intolerant to something in wheat specifically.

You may be able to safely consume gluten-containing products other than wheat—though it's worth pointing out that many of these products (primarily grains and processed foods) would not be foods you should be consuming regularly anyways.

3 Reasons Gluten Intolerance May Be More Serious Than Celiac Disease

As you can see, gluten intolerance is not a black-or-white issue, where you either have Celiac disease or you don't. There are several components of wheat that people can react to that are not covered by Celiac screening tests, and there is little doubt among those who are familiar with the scientific literature that non-celiac gluten sensitivity (NCGS) is a real condition.

Yet despite this, we continue to see headlines in the media like this:

- **Time for Some Grains of Truth About Gluten**
- **Eat More Gluten: The Diet Fad Must Die**
- **Why We're Wasting Billions on Gluten-Free Food**

These stories—and many other like them—argue that NCGS is rare, and that people who eliminate gluten from their diet are just silly fad followers. In this section, however, I'm going to present three reasons why NCGS is not only a bonafide condition, but may in fact be a much more serious problem than Celiac disease.

#1: CELIAC DISEASE IS FAR EASIER TO DIAGNOSE THAN NCGS

As I previously mentioned, some researchers estimate that there are 6.4 undiagnosed cases of Celiac disease for every diagnosed case—the majority of which are atypical or "silent" forms with no damage to the gut. (43) This silent form of CD is far from harmless; it is associated with a nearly fourfold increase in the risk of death. (44)

I believe that patients with NCGS are even more likely than patients with CD to go undiagnosed. Most gastroenterologists today know how to screen for celiac disease; they will typically test for antibodies to alpha gliadin, transglutaminase-2, deamidated gliadin, and endomysium, and if positive do a biopsy to determine if tissue damage is present.

But if you recall from the beginning of this eBook, we know that people can (and do) react to several other components of wheat, as well as other types of tissue transglutaminase found in the skin and the brain. (45, 46, 47, 48, 49, 50)

So, imagine a scenario where the patient is reacting to deamidated gliadin, glutenin, gluteomorphin, and either transglutaminase-3 or -6, but not reacting to alpha gliadin or transglutaminase-2—which are the antibodies used to screen for CD by most doctors. **They will remain undiagnosed, and may continue to eat gluten for the rest of their lives, putting themselves at serious risk for autoimmune and other diseases.**

This is not a hypothetical situation. In fact, I see cases like this all the time in my practice. Here is a screenshot from a test I ran on a patient. I use a much more thorough test for wheat and gluten intolerance called Array 3 from Cyrex Laboratories. Unlike other tests, it measures antibodies not only to alpha gliadin and transglutaminase-2, but also many of the other components of the wheat protein I mentioned above, as well as transglutaminase-3 and 6.

TEST	RESULT			
Array 3 – Wheat/Gluten Proteome Reactivity & Autoimmunity	**In Range (Normal)**	**Equivocal***	**Out of Range**	**Reference (ELISA Index)**
Wheat IgG	0.46			0.3-1.5
Wheat IgA	0.59			0.1-1.2
Wheat Germ Agglutinin IgG	0.82			0.4-1.3
Wheat Germ Agglutinin IgA	0.63			0.2-1.1
Native & Deamidated Gliadin 33 IgG			2.18	0.2-1.2
Native & Deamidated Gliadin 33 IgA			1.40	0.1-1.1
Alpha Gliadin 17-mer IgG	0.63			0.1-1.5
Alpha Gliadin 17-mer IgA	0.32			0.1-1.1
Gamma Gliadin 15-mer IgG	<0.50			0.5-1.5
Gamma Gliadin 15-mer IgA	0.29			0.1-1.0
Omega Gliadin 17-mer IgG	0.68			0.3-1.2
Omega Gliadin 17-mer IgA	0.34			0.1-1.2
Glutenin 21-mer IgG			1.74	0.1-1.5
Glutenin 21-mer IgA	0.76			0.1-1.3
Gluteomorphin + Prodynorphin IgG			1.35	0.3-1.2
Gluteomorphin + Prodynorphin IgA	0.50			0.1-1.2
Gliadin-Transglutaminase Complex IgG			2.00	0.3-1.4
Gliadin-Transglutaminase Complex IgA	0.62			0.2-1.5
Transglutaminase-2 IgG	0.87			0.3-1.6
Transglutaminase-2 IgA	0.76			0.1-1.6
Transglutaminase-3 IgG			1.68	0.2-1.6
Transglutaminase-3 IgA	0.94			0.1-1.5
Transglutaminase-6 IgG			1.63	0.2-1.5
Transglutaminase-6 IgA	0.72			0.1-1.5

This patient is not reacting to alpha gliadin or transglutaminase-2. Had they been tested by their conventional doctor, they would have been told that they do not have celiac disease or gluten intolerance. However, as you can see, she is reacting quite significantly to several different components of wheat, including:

- Native and deamidated gliadin and gluteomorphin, which are compounds produced during the digestion of wheat.
- Glutenin, which is the other major fraction of the wheat protein, along with gliadin.
- Gliadin-transglutaminase complex, which indicates that the patient is experiencing an autoimmune reaction to wheat.

- Transglutaminase-3, which is expressed primarily in the skin, and to a lesser extent in the brain and placenta.
- Transglutaminase-6, which is expressed in the brain and nervous system.

When this patient consumes wheat or other gluten-containing foods, she may not experience the classic digestive symptoms associated with CD or NCGS, because she is not producing antibodies to transglutaminase-2 (which is mostly expressed in the gut). Instead, her intolerance of wheat could manifest in skin conditions like eczema or psoriasis, and in neurological or brain-related conditions like depression, peripheral neuropathy, or ADHD. (51, 52)

Worst of all, if this patient had not had this test, and had continued to eat wheat and gluten for the rest of her life, it's likely that she would have been at much higher risk for the long list of serious conditions that are associated with gluten intolerance, such as multiple sclerosis, ataxia, diabetes, and even Amyotrophic Lateral Sclerosis (Lou Gehrig's disease). (53, 54, 55, 56)

Unfortunately, this patient is not the exception—she is the rule. I've seen so many test results just like this, where the patient would have been misdiagnosed as not having gluten intolerance had they gone to a conventional doctor.

This presents another obvious problem, of course: if very few health care providers are doing the correct testing for gluten intolerance (like the panel from Cyrex above), then how can we possibly know what the true prevalence of NCGS is? We can't—but given everything I've written above, we can certainly suspect that it's much higher than currently believed.

According to Cyrex Labs, 1 in 4 people that take the Array 3 panel test positive for some form of wheat or gluten intolerance. Granted, this is not a representative sample, since most people that take the Cyrex panel are dealing with chronic illness of some kind.

#2: CURRENT CULTURAL ATTITUDES TOWARD NCGS MEAN MORE PEOPLE WILL REMAIN UNDIAGNOSED

As I've already mentioned, there has been a big backlash in both the mainstream media and on social media channels against the idea of gluten intolerance. Despite overwhelming evidence to the contrary, uninformed journalists and armchair Facebook scientists continue to argue that NCGS is some kind of widespread collective delusion—

simply a figment of the imagination of anyone who claims to experience it. And for reasons that I do not fully understand, they do so with an almost religious fervor.

The "gluten intolerance haters" seemed to emerge in force after a paper published by Gibson et al. in 2013—which I discussed in a previous section—made the rounds in the media. If you recall, this study found that a group of patients with irritable bowel syndrome (IBS) were not sensitive to gluten, but instead were reacting to a group of poorly absorbed carbohydrates called FODMAPs. (57) Aside from the fact that this study did not in any way disprove the existence of NCGS, from a practical perspective the study findings would not have changed the behavior of most people with IBS who identified as being gluten intolerant, since wheat and many other gluten-containing grains are FODMAPs and should thus be avoided by these patients.

More importantly, however, in the last two years since the Gibson paper new studies have been published that directly contradict Gibson's findings and strongly suggest that patients with IBS do, in fact, react adversely to gluten—and not just FODMAPs.

For example, a new double-blind, randomized trial out of Iran was specifically designed to determine whether a group of IBS patients reacted to gluten specifically, or simply improved for other reasons on a gluten-free diet. (58) Here's how it worked:

1. 80 patients followed an "almost-gluten-free" diet (dietary compliance was considered optimal if consumption of gluten was below 100 mg/day, the equivalent of roughly 1/8 tsp of wheat four).
2. After six weeks, the 72 patients that complied with the diet and experienced significant improvement were then randomized into two groups: Group A, and Group B.
3. Group A (35 patients) was given a 100 g packet containing a gluten meal (free of FODMAPs). Group B (37 patients) was given a placebo packet (100 g) containing rice flour, corn starch, and glucose.
4. Patients in both groups consumed the powders for six weeks, while both groups continued on gluten-free diets.

After six weeks of the diet symptoms were controlled in only 26% of the gluten group, compared with 84% of the placebo group. In the gluten-containing group, all symptoms —especially bloating and abdominal pain—increased significantly one week after starting the gluten.

The authors point out that it is important to properly identify gluten intolerance and distinguish it from FODMAP intolerance because some recent research suggests that long-term low FODMAP diets may have adverse effects on the gut microbiome. One study found that a low FODMAP diet compared with a habitual diet reduced the proportion and concentration of Bifidobacteria, one of the most beneficial species of bacteria in the colon. (59)

But I would add another equally serious consequence of misdiagnosing gluten intolerance as FODMAP intolerance, which is the increase in risk for numerous and sometimes serious diseases that occurs when someone with NCGS continues to consume gluten.

#3: MANY DOCTORS AND PATIENTS AREN'T SERIOUS ENOUGH ABOUT NCGS TREATMENT

This last point is a natural consequence of the first two. If detecting NCGS in conventional medical settings is unlikely, and there is a strong cultural backlash against it, where does that leave the millions of people that are likely suffering from NCGS without even knowing it?

Even if they do suspect that they are gluten intolerant, they might be dissuaded from pursuing a strict gluten-free diet by their friends, social media contacts, or even their doctor, all of whom are likely uninformed on this subject and do not understand the deficiencies in conventional testing or the complexity of the topic.

Based on the research I've reviewed in this article, and several others I linked to here, **we should be more aggressive—not less—in diagnosing and treating gluten intolerance.**

We need greater access to test panels like Cyrex Labs Array 3, which is the only commercial test outside of a research setting that screens for antibodies to many of the proteomes in wheat, instead of just testing for alpha gliadin. We need better training for doctors on how to recognize the myriad of symptoms and conditions associated with gluten intolerance, so they don't make the common mistake of assuming that the patient isn't gluten intolerant if they don't have digestive problems. And we need some prominent journalists to educate themselves, step forward, and take responsibility for treating this as the serious, potentially life-threatening problem that it is.

Even without access to tests like Array 3, an elimination/provocation trial where gluten is removed completely from the diet for 60 days and then reintroduced is still considered to be an accurate method of assessing gluten intolerance. Doctors should be much more proactive about recommending this to patients, and despite the claims of some mainstream nutritionists and dietitians to the contrary, there is no risk to removing gluten from the diet. (60)

Finally, it's worth pointing out that many people that are intolerant of gluten are also intolerant of other food proteins found in foods like dairy, eggs, and unfortunately, coffee. Studies have shown that about 50 percent of patients with CD show intolerance to casein, a protein in milk. (61)

This may explain why up to 30 percent of CD patients continue to have symptoms or clinical signs after adopting a gluten-free diet. (62) For this reason, I recommend a completely grain- and dairy-free diet during the gluten challenge period.

Has Antibiotic Overuse Caused a Celiac Disease Epidemic?

Non-celiac gluten sensitivity may have stolen the media spotlight, but there's no denying that its more socially-acceptable cousin Celiac disease is more prevalent now than ever. In the US, rates of CD have increased at least 5-fold over the past few decades, and prevalence in Finland has doubled. (63, 64, 65) The incidence of CD has also increased four-fold in the UK and three-fold in the Netherlands in the past 20 years, and the incidence of pediatric CD in Scotland has increased 6.4-fold. (66, 67, 68)

So naturally, everyone is wondering – why? We know that there's a strong genetic component to celiac disease (and our ability to detect the disease has vastly improved), but the rising rates have occurred too quickly to be explained by a genetic shift in the population.

Besides, the genes that predispose an individual to CD are actually relatively common in the population, but only a very small percentage of those people actually develop the disease. In other words, genetics appear to be necessary – but not sufficient – for someone to develop CD.

ANTIBIOTICS CAN CAUSE INTESTINAL DYSBIOSIS AND INFECTION

Clearly, something has changed in the environment to trigger celiac disease in a higher proportion of genetically susceptible people. Multiple factors probably play a role, but evidence indicates that one big factor is the intestinal microbiota. And a major contributor to disordered intestinal microbiota is antibiotic overuse.

In **an article I wrote** on the effects of antibiotics, I reviewed several studies that demonstrate how drastically antibiotics can alter the gut microbiome. Just a single course of antibiotics can reduce the richness and diversity of the intestinal microbiota, and in many cases, people never completely regain the diversity they lost.

Even if a person doesn't develop an overt, clinically-diagnosable infection such as C. difficile, imbalances in the types of bacteria that colonize the gut can still cause serious problems. But to understand how antibiotic-induced gut dysbiosis could trigger celiac disease in genetically-susceptible individuals, it will help to review some of the basic mechanisms behind celiac disease.

CELIAC DISEASE INVOLVES AN IMMUNE REACTION TO BOTH GLIADIN AND TISSUE TRANSGLUTAMINASE

The biological mechanisms behind celiac disease are complicated and still not fully understood, but the general idea is that gluten – a group of proteins found in wheat, rye, and barley – triggers an autoimmune response that results in severe damage to the epithelial lining of the intestine.

If you recall from the first section of this eBook, gliadins and glutenins are the two main components of gluten, with gliadins being the primary trigger for celiac disease. These proteins are very difficult for the body to digest fully, but in most people, this isn't a problem. However, in people with celiac disease, certain cells (known as "antigen-presenting cells") get a hold of these large, undigested fragments of protein and present them to T-cells, triggering an immune response. (**69**, **70**)

An enzyme called tissue transglutaminase (TG2) is also important in the development of CD. This is because antigen-presenting cells only bind certain types of proteins, and they don't usually bind normal gliadin fragments. (**71**) On the other hand, TG2 readily binds gliadin, and actually modifies it to make the gliadin much more attractive to antigen-presenting cells. This vastly increases the likelihood of an immune response.

Once this happens, the body starts creating antibodies against gliadin. But because the gliadin is usually bound to TG2, the body also creates antibodies against TG2, its own enzyme. This attack of "self" is what earns CD the classification of "autoimmune."

INTESTINAL DYSBIOSIS AND INFECTION CAN LEAD TO UP-REGULATION OF TISSUE TRANSGLUTAMINASE

In healthy individuals, TG2 plays a role in tissue repair, as well as in other processes such as regulation of cell death; it's not an enzyme that's "supposed" to interact with gluten. (Interestingly, TG2 also plays a role in other diseases, such as Parkinson's and Huntington's, by modifying proteins that it isn't supposed to modify.) (72)

Most TG2 appears to be either stored safely inside cells or inactive under normal conditions, and is only activated in the event of tissue injury, bacterial or viral infection, or another source of inflammation. (73, 74) This indicates that tissue damage or inflammation in the intestine (and subsequent TG2 up-regulation) might actually be necessary for the development of CD.

Without substantial TG2 activity, it's unlikely that the antigen-presenting cells would bind and present enough gluten fragments to provoke a major immune response. But a bacterial or viral infection could create inflammation and tissue damage that would activate TG2, and thus trigger the cascade of events eventually leading to celiac disease.

INTESTINAL DYSBIOSIS AND INFECTION CAN CONTRIBUTE TO LEAKY GUT

Another factor to consider is the location of tissue transglutaminase. Nearly all TG2 is found in the sub-epithelial region of the intestine, a place that gluten shouldn't have access to. This means the intestinal barrier would need to be compromised in some way for gluten proteins to significantly interact with TG2. (75)

This fits with previous work done by researchers such as Alessio Fasano, who have **hypothesized** that a person cannot develop an autoimmune condition such as CD if they don't have leaky gut. If the intestinal barrier is intact, the immune system will never "see" the antigens, so it won't mount an immune response.

But one big risk factor for developing leaky gut is intestinal dysbiosis or infection. Bacterial components such as lipopolysaccharides can induce inflammation and

increase intestinal permeability, which would allow gluten into the sub-epithelial region of the intestine where it could be modified by TG2 and trigger CD. (76)

CANDIDA INFECTION MAY TRIGGER CELIAC DISEASE THROUGH CROSS-REACTIVITY

So far, we've been talking about dysbiosis in a general sense, but there's evidence that specific microbes could trigger celiac disease as well. One study (hat tip to **Questioning Answers** for the find) found that an overabundance of the yeast Candida albicans could contribute to the development of CD, and unfortunately, antibiotic use is a big risk factor for developing a candida infection. (77)

Candida is a normal part of the intestinal microbiome of healthy individuals, but problems can arise when it overgrows relative to other inhabitants of the intestine. Remember how tissue transglutaminase (TG2) readily binds gliadin? Well, it turns out that candida expresses a protein named Hwp1 that also binds TG2, potentially leading to immune activation and cross-reactivity with gluten.

The study found that people without CD who had candida infections produced anti-gliadin antibodies, as well as the expected anti-Hwp1 antibodies. People with CD produced antibodies to both proteins as well. This means that in theory, a person who is genetically susceptible to CD but who doesn't have the disease could develop the disease in response to a candida infection.

SO, WHAT DOES THIS MEAN FOR YOU?

As you can see, there are several ways in which antibiotic overuse and subsequent intestinal dysbiosis or infection could lead to the development of celiac disease. And although non-celiac gluten sensitivity does differ from celiac disease in its development and presentation (primarily in that it doesn't involve a reaction to TG2), it's likely that antibiotic overuse plays a role in the increasing prevalence of NCGS as well. The development of both CD and NCGS involve immune reactions to normally-harmless antigens found in gluten, and although the role of epithelial barrier function is less well understood in NCGS, it is apparent that the balance of intestinal microbiota plays a significant role in disease pathogenesis. (78)

As I've said before, antibiotics can be lifesaving and are necessary in some situations, but that doesn't mean they're free of consequences. It's becoming more and more clear how vitally important it is to use antibiotics responsibly, whether that's **not using them**

at all, or properly rehabilitating the gut during and after a course when they're deemed necessary.

Final Thoughts

In my book, The Paleo Cure (previously published as Your Personal Paleo Code), I argued that there are three categories of response to gluten:

- Tolerance
- Non-celiac gluten sensitivity, aka "gluten intolerance"
- Celiac disease

I don't believe that gluten is responsible for all chronic illness in all people, as some have seemed to suggest. But I think the research clearly supports the existence of non-celiac gluten sensitivity, and if anything, it is significantly under-diagnosed.

As you've learned, gluten intolerance can cause a huge variety of symptoms aside from the digestive symptoms that you might expect, and conventional screening methods miss the vast majority of cases. Your best bet for determining whether you have NCGS is either to test yourself with an elimination/provocation trial where gluten is removed completely from the diet for 60 days and then reintroduced, or to find a practitioner who can order the Cyrex Labs Array 3 for you.

You may be hesitant to get tested for gluten intolerance if you don't have digestive symptoms, especially with the societal backlash against the new gluten-free "fad," but if you have other symptoms—particularly neurological or skin conditions—that you just can't figure out, I strongly encourage you to at least do a gluten elimination trial. (Check out my 14Four program for a great way to get started with this.)

Left untreated, gluten intolerance can lead to serious and debilitating health conditions, so discovering and addressing a sensitivity can save your future health as well as improve your current quality of life.