GLUTEN SENSIVITY AND ITS ROLE IN CHRONIC FATIGUE AND AUTOIMMUNE DISEASE

WHAT YOU NEED TO KNOW

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Toward Healing the Planet,
One Person At A Time

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INTRODUCTION

Even a short scan of the published medical literature on the impact of diet, specifically food allergies and sensitivities, on Chronic Fatigue Syndrome (CFS), also known as Myalgic Encephalomyelitis (ME), would lead you to conclude that dietary modifications have no impact on either the onset of or a recovery from the illness.

Back in 1996 researchers in the *Journal of the American Dietetic Association* found no specific nutrient deficiencies in ME/CFS and concluded diet did not play a role. Dietary guidelines for ME/CFS remain as those recommended by the Center For Disease Control (CDC) in the US and abroad; CFS patients should simply follow the official government "balanced diet" guidelines which promotes high levels of starchy carbohydrates like gluten-containing breads and cereals.

Could they be missing something? I propose that two disorders associated with sensitivity to the gluten products in grains, Celiac Disease (CD) and Non-Celiac Gluten Sensitivity (NCGS), are vastly under diagnosed both in the general and CFS population. In fact, studies suggest undiagnosed Gluten Sensitivity contributes to early mortality.

Celiac Disease– refers to people with total villous atrophy in the gut as a result of immune sensitivity to gluten (gliadin), which has resulted in autoimmune antibodies to the gut lining.

Non-Celiac Gluten Sensitivity – includes broadly two classes of people. First, those with only partial villous atrophy or inflammation in the gut (which the current test for CD misses) induced by sensitivity to gluten, and second, people with no gut imbalances at all but autoimmunity to other organs and systems (e.g. thyroid) induced by sensitivity to gluten.
"CD is a much greater problem than has previously been appreciated" Archives of Internal Medicine February 2003

Autoimmunity and Celiac Disease

Autoimmune disorders are now cumulatively the third leading cause of death in the industrialized world. Recognized in about 24 million people, autoimmune disorders are now the leading cause of death in the U.S. (and those are only the ones that have been diagnosed).
While many individual autoimmune diseases are rare, collectively they are thought to affect approximately 8 percent of the United States population – 24 million persons.
To provide a context to evaluate the impact of autoimmune diseases, cancer affected approximately 9 million people and heart disease affected approximately 22 million people in the United States.
"Gluten sensitivity is a systemic autoimmune disease with diverse manifestations" *Lancet Neurology* March 2010

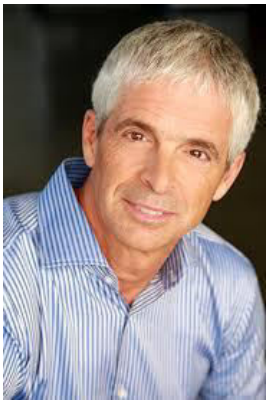
With diagnostic rates at about 1 out of 3 people, some form of autoimmunity is probably present in at least 72 million people in the US.
NIH. Autoimmune Diseases Coordinating Comm.Autoimmune Diseases Research Plan 2006

You are 10 times more likely to develop an autoimmune disorder if you have CD.

Yes, you read that right. As you will read below, both untreated Celiac and NCGS appear to significantly increase mortality rates and CD is being implicated in almost all autoimmune disorders.

More than 19,000 papers on CD and the new entity NCGS have been published in PubMed. Despite (or maybe because of) the voluminous data, no one has worked on connecting the dots and synthesizing the results in a way that both patients and busy practitioners can get. This is where my role comes in as a formerly busy physician and functional medicine specialist.

Dr Tom O'Bryan



I specialized in the treatment of Celiac and NCGS before giving it up to train other Doctors and practitioners on this subject around the world full-time. You might say…I am on a mission.

In this eBook, I aim to summarize key information from the training presentations I gave in the UK in 2011 to nutritional therapists and medical doctors.

I can almost guarantee your doctor, gastroenterologist or even your specialist ME/CFS doctor doesn't know much of this information and probably doesn't grasp its potential significance in ME/CFS.

Surprised that Diet Could Play a Significant Role in Such a Serious Disease as Chronic Fatigue Syndrome?

Patients and practitioners alike may be surprised that diet can play a critical role in serious chronic complex illnesses such as ME/CFS. Some may even feel downcast that "just diet" and not a virulent bug could be the cause or a major contributor to their ME/CFS.

Misconception and Misdiagnosis

Misperceptions regarding the nature of food 'allergy' that still permeate much of the medical world are at the root of this. 'Classical' approaches to understanding food allergies assume reactions to food can only be IgE mediated. IgE produces classic allergic reactions such as: sneezing, sniffling, rashes and difficulty breathing. We know from the research, that IgE food allergies are likely to play only a small role in ME/CFS patients.

Celiac disease (CD) and non-celiac gluten sensitivity (NCGS), however, are IgG and IgA mediated immune responses that can cause chronic gut inflammation, and very likely chronic inflammatory and autoimmune processes elsewhere in the body.

The Inflammatory Disease 'Epidemic'

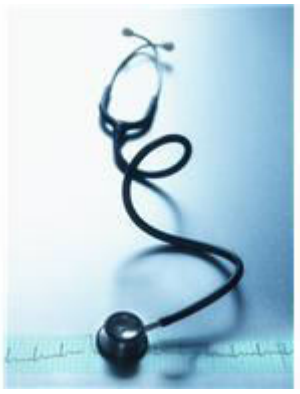
Inflammatory disorders have been increasing rapidly over the past thirty years. Chronic inflammation and autoimmune processes are implicated in ALL of the major chronic complex illnesses that blight humans today. The studies covered in this eBook suggest a 'fire in the gut' i.e., untreated gut inflammation may increase the risk of early mortality in all major chronic illnesses.

For a variety reasons covered later, including the intriguing evidence that at least a subgroup of the ME/CFS population has an autoimmune disorder, the facts about CD and NCGS need to be fully understood.

10 FACTS YOUR DOCTOR OR GASTEROENTEROLOGIST PROBABLY DOESN'T KNOW ABOUT CELIAC DISEASE AND NON GLUTEN CELIAD SENSITIVITY (NCGS)

"…for every symptomatic patient with celiac disease there are eight patients with celiac disease and no gastrointestinal symptoms." *Gastroenterology* February 2001

FACT 1: Due to a historical misconception that Celiac Disease (CD) MUST present with gastrointestinal (GI) symptoms, CD is not tested for in many patients, and thus is vastly underdiagnosed.



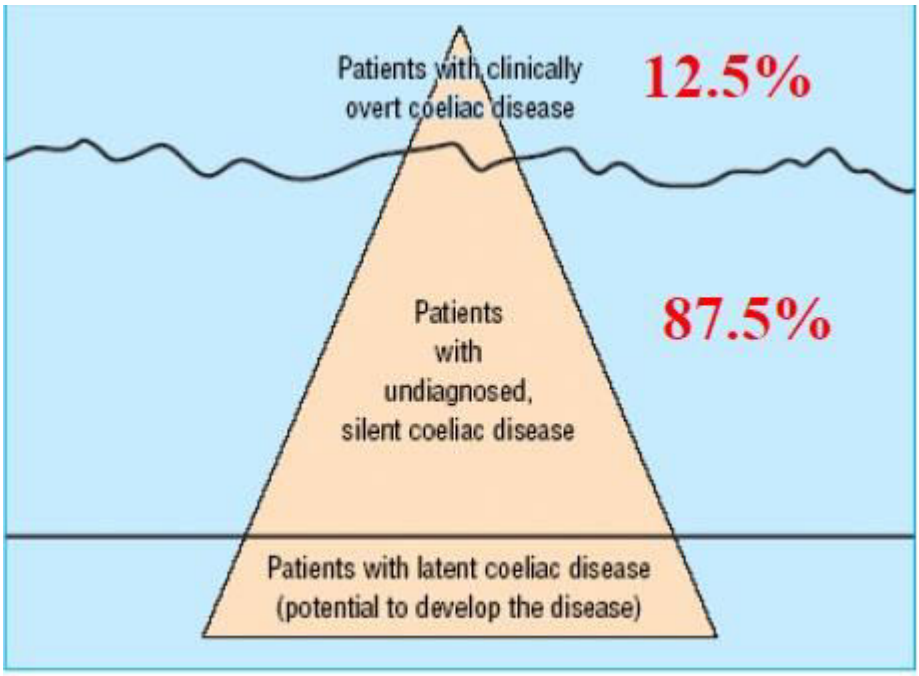
The chances are if you have few or no GI symptoms, your Doctor won't have tested you for CD. Nor is CD part of the differential diagnosis for ME/CFS. Unfortunately, doctors don't realise that neurological symptoms and a wide range of other non-GI symptoms, most of which are found in ME/CFS, should trigger the test for CD.

The current guidelines for celiac disease suggest testing for it where there is*" chronic fatigue, short stature, delayed puberty, dental enamel defects, elevated liver transaminase levels, dermatitis herpetiformis, and nutritional anemias..."*

The brain seems to be particularly vulnerable… *Pediatrics*August 2001

CD was originally believed found in people with diarrhea, cramping, bloating, constipation and other gastrointestinal issues, stool problems, anemia and weight loss. **Further research revealed CD and its offshoots commonly cause fatigue, weakness, osteoporosis, joint and bone pain, migraines, numbness and tingling, depression, etc.**

"The iceberg is a common model used to explain the epidemiology of coeliac disease. The majority of patients have what is termed silent coeliac disease, which may remain undiagnosed because the condition has no (GI) symptoms." British Medical Journal July 1999



Iceberg model depicting prevalence of coeliac disease

Although celiac disease has been known for over thirty years to cause both gastrointestinal and neurological symptoms, it took until 2000 before celiac disease was shown, in some individuals, to cause only neurological symptoms. As late as 2010, a review article in Lancet, no less, noted that 'only recently' has it been accepted that celiac disease can present with only neurological symptoms. In fact, it appears that most people with CD who have neurological symptoms don't have gastrointestinal symptoms.

FACT 2: A Diagnosis of celiac disease refers to the END STAGE of the disease and diagnosis of celiac disease requires TOTAL VILLOUS ATROPHY. CD takes YEARS to manifest and is preceded by GUT INFLAMMATION. These earlier stages may be described as part of Non-Celiac Gluten Sensitivity (NCGS), but like celiac disease also, still mostly go undiagnosed and untreated.

If you had a negative test for CD that means you didn't have total villous atrophy. You could, however, have partial villous atrophy or increased lymphocyte activity in the gut lining which standard testing for CD misses.

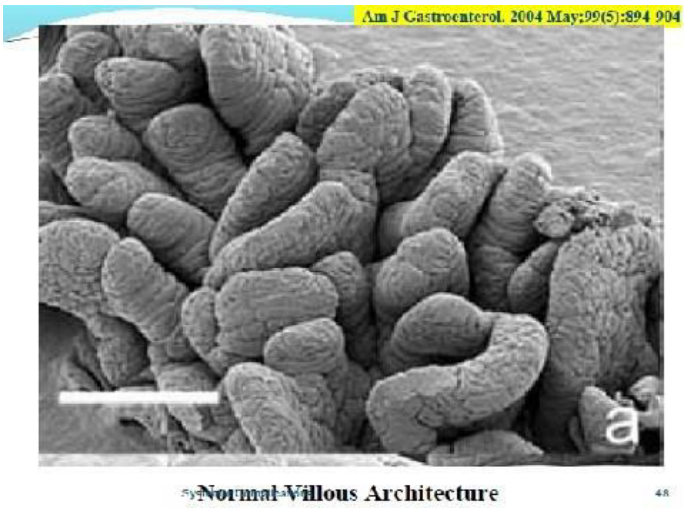
The villi, with their finger-like projections, appear like shag carpets in the gut. The villi, with their high surface area, maximise nutrient absorption from the gut.

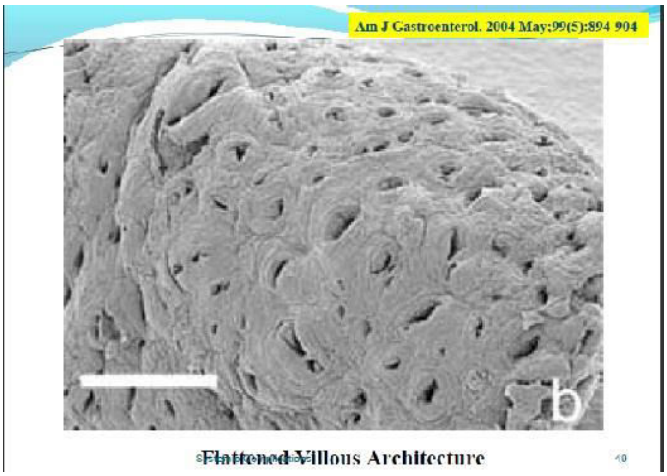
If you have partial villous atrophy or no villous atrophy at all, your CD test will be NEGATIVE.

A large amount of inflammation in the gut can still occur in people not testing positive for CD. In fact, it's clear that the processes that result in total atrophy of the villi begin much, much earlier and are often evident if they are looked for. In fact, some researchers believe the search for the roots of celiac disease should begin early in life, perhaps *even in utero* .

Normal vs Atrophied Villi

Normal looking villi are on the left; total villus atrophy (required for coeliac disease diagnosis)





Total villous atrophy doesn't occur overnight. The gut inflammation (mucosal intraepithelial lymphocytosis) that usually precedes the war zone-like structures occurring in total villus atrophy, can be identified. The lymphocytes shown in brown below, are producing the cytokines that will eventually destroy the intestinal villi, leading to "total villous atrophy" or "CD."

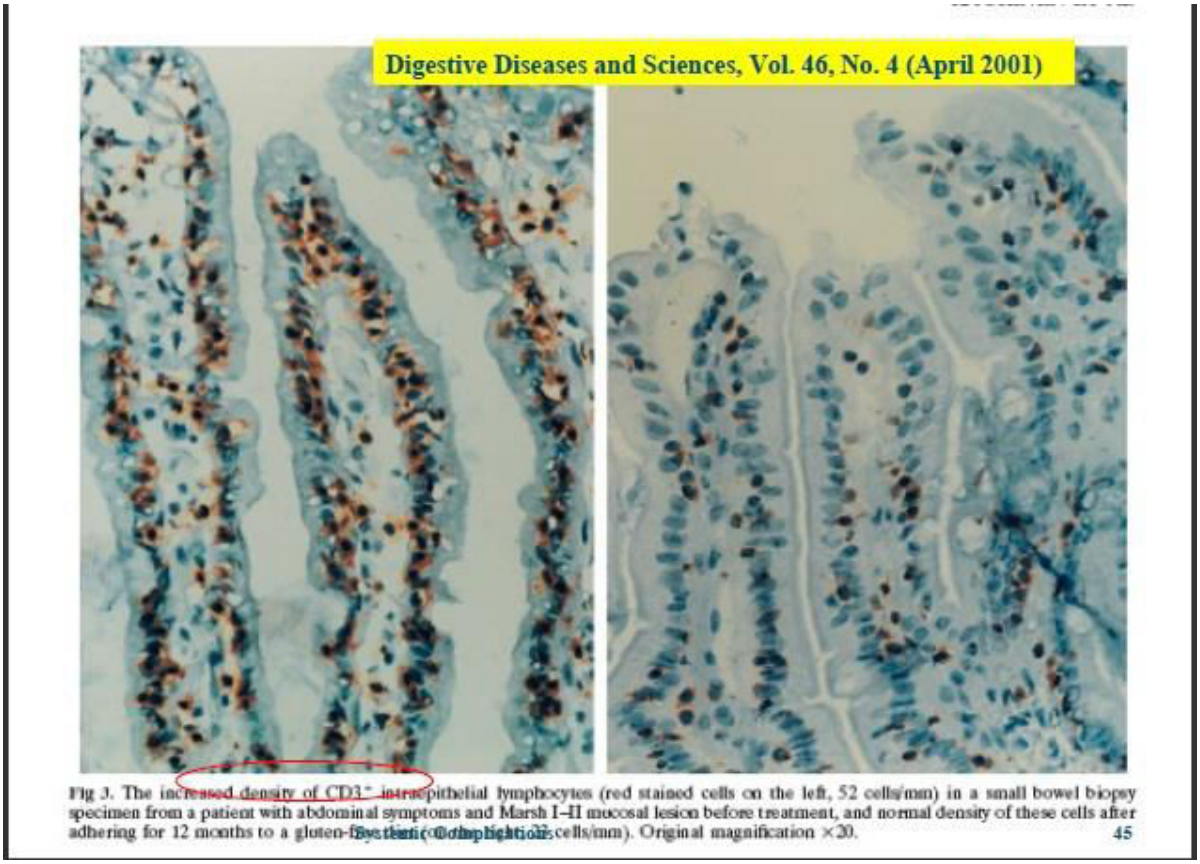


Fig 3. The increased density of CD3+ intraepithelial lymphocytes (red stained cells on the left, 52 cells/mm) in a small bowel biopsy specimen from a patient with abdominal symptoms and Marsh I–II mucosal lesion before treatment, and normal density of these cells after adhering for 12 months to a gluten-free diet (right, 22 cells/mm). Original magnification ×20. 45

Indeed, studies suggest that the degree of lymphocyte invasion present is a more effective and certainly earlier test for gluten sensitivity than charting the degree of atrophy of the villi. Inflammation (lymphocyte invasion) comes first, followed by damage to the villi, followed by destruction (atrophy) of the villi.

The presence of gluten induced autoantibodies is another early test which, if the person keeps consuming gluten, appears to be able to predict the ultimate demise of their villi – (and their ultimate diagnosis with celiac disease).

If we include now not only all CD, but also all those with NCGS, how many people suffer from some form of gluten sensitivity?

312 family members (FMs) of CD disease patients were tested for **all types** of gluten sensitivity i.e.: CD, subclinical and silent forms. **1 out of 5 FM tested positive – suggesting 20% of the population have some form of gluten sensitivity.**

"We found a high-prevalence of CD between CD FMs, and most of them were olygo- or asymptomatic."
European review for medical and pharmacological sciences June 2010.

FACT 3: Untreated Celiac Disease (CD) and Non Celiac Gluten Sensitivity (NCGS) Is Associated with Increased Mortality Rates.

Your mortality rate is HIGHER with NCGS and CD and does not require the end-stage of total villous atrophy.

"The elevated mortality risk for all causes of death combined, reflected for the most part, disorders characterized by immune dysfunction" *Archives of Internal Medicine* July 2003

A large Swedish Inpatient Registry study investigating mortality risks in more than 10,000 CD patients over 30 years found having CD increased the risk of death from a plethora of major diseases. The study examined standardized mortality ratio (SMR), which charts the increased likelihood of death if you have both CD and another disease. The SMR of 11.4, for instance, in non-Hodgkins Lymphoma (NHL), for instance, indicates a person with CD and NHL is 11.4 times more likely to die earlier from Non-Hodgkins lymphoma than someone with that disease and no CD.

Note that most of these disorders are associated with immune dysfunction.

- *"Non-Hodgkins Lymphoma (SMR 11.4)*
- *Cancer of SI (SMR 17.3)*
- *Inflammatory Bowel Diseases (SMR 70.9)*
- *Autoimmune Diseases (including RA) (SMR 7.3)*
- *Diffuse disease of Connective Tissue (SMR 17.0)*
- *Allergic Disorders (i.e. asthma) (SMR 2.8) Diabetes (SMR3.0)*
- *Disorders of Immune Deficiency (SMR(20.9) Tuberculosis (SMR 5.9)*
- *Pneumonia (SMR 2.9)*
- *Nephritis (SMR 5.4)"*

The largest ever study of mortality rates found celiac disease in almost 10% of 350,000 plus biopsies collected over 40 years, 'latent' CD (normal mucosa but positive blood work) in about 1% (3.7K), and inflammation but still partially intact villi in about 5% (13K) of the biopsies .

Results showed increased mortality rates in all three cohort groups; startlingly, mortality rates were highest in **the inflammation (Non-Celiac Gluten Sensitive) group.**

•HRs in Coeliac disease (HR, 1.39; 95%) (i.e. **39%** more likely to die earlier)
•HRs in latent Coeliac disease (HR, 1.35; 95%) (**35%** more likely to die earlier)
•**HRs in patients with inflammation (HR, 1.72; 95%)** (**72%** more likely to die earlier)

When Ignorance is Not Bliss

"Individuals with Coeliac disease are treated with a gluten-free diet, while very few with inflammation are. Those with inflammation may have an overall worse prognosis than those with villous atrophy, since institution of a gluten-free diet often leads to normalisation of the mucosa." Journal of the American Medical Association Sept 2009

What could account for such a large increase in mortality in what appeared to be the least severely affected group? Proper diagnosis. In the study authors suggested that people with celiac disease tend to get diagnosed and heal their gut. People with NCGS, however, often don't get diagnosed. In their case, it's not the celiac disease that gets them but the long-term inflammatory state that increases their risk of dying from another disorder.

Focus on Children

"Children diagnosed with Coeliac disease had a threefold increased risk of long-term mortality. This is in marked contrast to the experience of adult Coeliac disease where the long-term increase of mortality was modest. The increased mortality in children from external causes may reflect behavioural change associated in coping with a chronic disease and its treatment."
American Journal of Gastroenterology April 2007

FACT 4: Having CD/NCGS and not adhering to a gluten free diet increases your risk of death 6 fold. The equivalent of 1/90th of a slice of bread can cause severe symptoms in the most sensitive. CD/NCGS is PERMANENT

"Death was most significantly affected by diagnostic delay, pattern of presentation, and adherence to the GFD…Non-adherence to the GFD, defined as eating gluten once-per-month increased the relative risk of death 6-fold…Our results emphasize the need for prompt diagnosis and treatment also in those patients with a minor or symptomless form of coeliac disease."
Lancet 2001

A Lancet study following up 1072 adult celiacs and 3384 first-degree relatives after 20 years found the SMR of 2.0 (200%) i.e. if you have CD you are twice as likely to die early than someone without it. Remarkably, eating even small amounts of gluten, placed celiacs at increased risk of death.

Gluten Sensitivity is Permanent

"Coeliac Disease is a permanent intolerance to gluten that results in immunologically mediated inflammatory damage to the small intestine mucosa" *American Journal of Clinical Nutrition* March 1999

Gluten-related disorders are **permanent;** while your gut may heal, your gluten sensitivity remains and adding gluten back into your diet will cause the inflammation to rear up again. Studies have found that even after five years on a gluten free diet, the gut will eventually flare up if you return to eating gluten products.

In some cases, even very small amounts of gluten can cause system-wide problems.

"A milligram of gluten a day keeps the mucosal recovery away: a case report"
Nutrition Review in Sept 2004

A frustrated 34 year old woman went to a Celiac specialist to find out why, after following a gluten-free diet for a year she was still not better. Testing revealed her antibodies were still sky high and she had total villus atrophy and osteoporosis.
She was suffering from hair loss, poor skin and chronic fatigue, but had a good attitude. The specialist asked how strict her gluten-free diet was. After being told she was still eating the odd amount every month, she was told to cut out gluten completely. A year later her energy was a bit better and her antibody results were high normal instead of sky-high, but her endoscopy results were still bad and she still had hair loss and osteoporosis.
The specialist agreed she was indeed on a gluten free diet but then discovered the lady was a Nun, and she was eating a small piece of host (sacramental bread) daily. The specialist met the priest and asked for a sample of the host. The specialist measured it and found that a 30 mg fragment of wafer contains approximately 0.5mg of gliadin (1 mg of gluten).
The woman refused to give up her daily sacrament until her priest prevailed on her to do so. Eighteen months later the woman came back *radiant* with a full head of hair, a healthy small intestine and no chronic fatigue.

The fragment of the wafer was half a thumb size.

FACT 5: Autoimmune Disorders occur ten times more commonly in people with celiac disease (CD) than in the normal population. CD triggers the production of autoimmune antibodies that attack other organs. CD initiated autoimmune disorders are likely to be misdiagnosed. (CD is also correlated with many non-Autoimmune Disorders.)

"Autoimmune diseases are the third leading cause of morbidity and mortality in the industrialised world, surpassed only by cancer and heart disease."
Annals of the rheumatic diseases Sept 2007

Autoimmune disorders are believed to affect approximately 8 percent of the US population or 24 million people. That's more people than are affected by heart disease (22 million) or cancer of all forms (9 million). This suggests autoimmune disorders may be the number one cause of death in the U.S.
NIH. Autoimmune Diseases Coordinating Comm.Autoimmune Diseases Research Plan. 2006

"Autoimmune disorders occur 10 times more commonly in CD than in the general population." The autoimmune disorders most frequently associated with CD are type 1 diabetes mellitus and autoimmune thyroiditis. The presence of celiac disease in type I diabetes, for instance, is approximately twenty-times higher than in the general population. The autoimmune antibodies associated with CD include anti-endocrine, anti-gastrointestinal, anti-nuclear, anti-cytoskeleton and anti-neurological antibodies.

CD is believed to trigger autoimmunity through a variety of mechanisms including HLA and non-HLA genes, mimicry, altered intestinal permeability, epitope spreading and others. One study suggested long duration exposure to gluten products is associated with higher rates of autoimmunity in celiac disease.

The longer celiacs are exposed to gluten the greater the risk they have of developing an autoimmune disorder.

"Our data show for the first time that the prevalence of autoimmune disorders in Coeliac disease is related to the duration of exposure to gluten"
Gastroenterology August 1999

The age the patient was Diagnosed with CD	The presence of other autoimmune condition in addition to CD
2	5%
2-4	11%
4-12	17%
12-20	27%
>20	34%

Unfortunately most people with celiac disease spend 5-10 years going from doctor to doctor before a correct diagnosis is made.

Other Disorders

CD is linked with many other diseases including liver and heart diseases, osteoporosis, myopathies, schizophrenia, small- fibre neuropathy and more: Celiac disease was associated with an 8-fold increased risk of death from liver cirrhosis. A gluten free diet, however, normalizes the levels of serum transaminases *in* 75% to 95% of patients with CD. One study found osteoporosis patients. In fact, the rate of celiac disease in osteoporosis is high enough that some recommend all osteoporosis patients undergo CD screening.

CD triggered inflammation appears to possibly cause or contribute to myopathy, a muscle disorder characterized by muscle weakness. A large epidemiological study involving almost 80,000 individuals suggested that **every type of cardiovascular disease** (heart attack, heart failure, stroke, etc.) is increased in patients with untreated celiac disease.

CD may increase risk factors for mental disorders such as schizophrenia. One research study proposes that schizophrenia is rare in cultures with low gluten consumption. Another population study, however, did not find a link between schizophrenia and CD. Rates of depression in CD and gastrointestinal disorders do not appear to be increased relative to healthy controls.

Peripheral Neuropathy

IgG antibodies were present in 34% and biopsy demonstrated villi destruction (celiac disease) in 9% of people with idiopathic peripheral neuropathy including small-fiber neuropathy. (Another study, however, concluded the two were not linked.)

However, a large Swedish study involving 14,000 people with celiac disease and 70,000 healthy controls found increased risk of peripheral neuropathy (but not increased risks of neurological disorders such as Parkinson's, Alzheimer's, multiple sclerosis, Huntington's disease and myasthenia gravis). In the study, authors suggested people with peripheral neuropathy be

tested for CD. Recent studies suggest a form of peripheral neuropathy called small fiber neuropathy is common in fibromyalgia.

Gluten sensitivity was present in a third of patients with sensory ganglionopathy, a disorder characterized by damage to the cranial and spinal ganglia, usually by autoimmune processes. Autopsies of the three gluten sensitive, SG patients indicated damage to the dorsal ganglia.

Swedish Studies

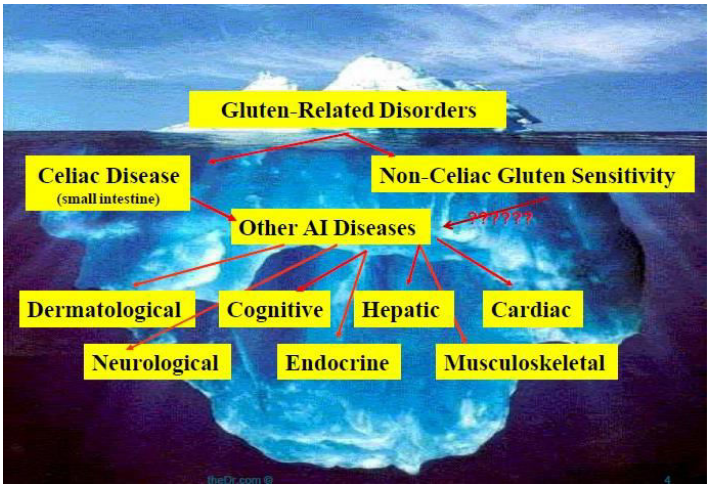
Sweden has put its large medical databases to good use in many celiac studies.

Adult celiac disease was associated with increased risk of pancreatitis in another Swedish study. A large Swedish study found celiac disease to be associated with increased risk of a raft of liver diseases including hepatitis, liver failure, primary biliary cirrhosis, liver cirrhosis and fibrosis and fatty liver.

Rates of depression increased after celiac disease (but not before it). Immune dysfunction in both celiac disease and sarcoidosis was believed to play a role in increased rates of sarcoidosis in people with celiac disease. Immune dysfunction and inflammation was believed to be behind increased rates of kidney disease as well. Even fractures got in the act with the Swede's finding increased risk of hip and other fractures in people with CD. Increased risks were also found in diabetes (relatively low risk), thyroid disease and adrenal disease (greatly increased).

FACT 6: NCGS may trigger autoimmunity via gut inflammation or via molecular mimicry - with no gut involvement at all.

…When the finely tuned trafficking of macromolecules is dysregulated in genetically susceptible individuals, both intestinal and extraintestinal autoimmune disorders can occur…
Nature clinical practice. Gastroenterology &hepatology Sept 2005



Although research has yet to confirm the link between autoimmunity and NCGS, the largest study ever completed on gluten sensitivity suggests mortality rates are higher for people with non-celiac gluten disorder (NCGS) than Coeliac disease (CD). That suggests it's probably just a matter of time before similar correlations regarding autoimmunity are made in the literature.

Indeed, the study found that people with gut inflammation (which is characteristic of NCGS) are also highly likely to suffer from "leaky gut" which is strongly associated with the onset of autoimmune disorders.

The GI tract regulates the flow of macromolecules between the gut and the rest of the body. Some researchers believe the introduction of harmful macromolecules into the blood stream commonly triggers autoimmune processes both, inside or outside of the gut.

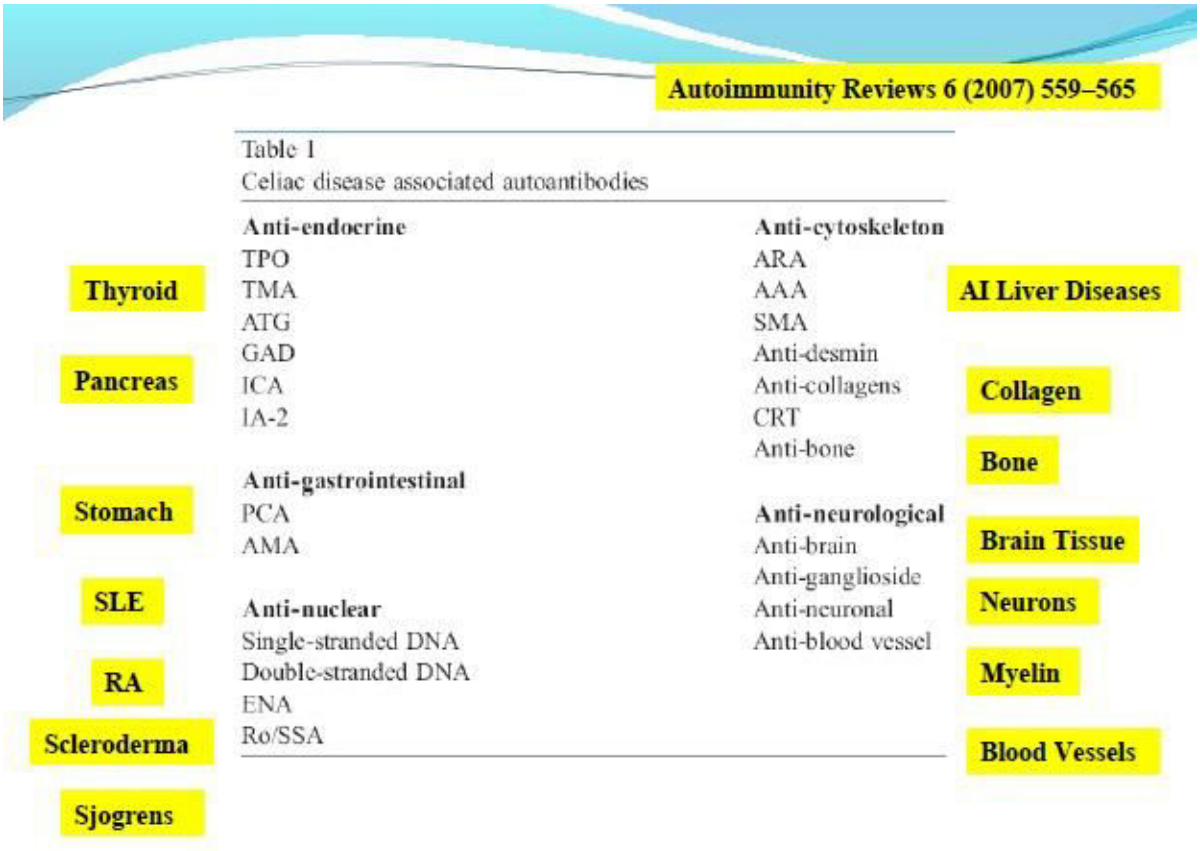
It is also important to understand that even if your gut exhibits no villous atrophy (celiac disease), and no intraepithelial lymphocytosis (inflammation) in the gut, you can still test positive for gluten sensitivity (positive IgA and IgG blood tests to gluten) and your gluten sensitivity may be triggering increased autoimmune antibodies to a whole range of different organs in the body.

Which specific antibodies you develop may depend on your individual genetic make-up or "weak-link" in the chain.

"Antigenic mimicry" is one method it's thought that CD causes autoimmunity to organs outside the gut. As the body becomes sensitised to gluten, it can start to attack a range of molecules that are similar to gluten, like those associated with the thyroid gland.

"The common immunogenetic theories ….are sharing common HLA and non-HLA genes, antigenic mimicry, damage-induced neoantigen exposure, altered intestinal permeability, idiotype network dysregulation and epitope spreading."
Autoimmunity Reviews Sept 2007

The below autoantibodies have been associated with CD; notice that most do involve the gut.



Autoimmunity Reviews 6 (2007) 559–565

Table 1
Celiac disease associated autoantibodies

Anti-endocrine	Anti-cytoskeleton
TPO	ARA
TMA	AAA
ATG	SMA
GAD	Anti-desmin
ICA	Anti-collagens
IA-2	CRT
	Anti-bone
Anti-gastrointestinal	
PCA	**Anti-neurological**
AMA	Anti-brain
	Anti-ganglioside
Anti-nuclear	Anti-neuronal
Single-stranded DNA	Anti-blood vessel
Double-stranded DNA	
ENA	
Ro/SSA	

Thyroid
Pancreas
Stomach
SLE
RA
Scleroderma
Sjogrens
AI Liver Diseases
Collagen
Bone
Brain Tissue
Neurons
Myelin
Blood Vessels

According to the latest textbook: *Advancing Medicine with Food and Nutrients* 2nd Edition, correlations between the illnesses below and NCGS have been confirmed in the literature:

- IgA Nephropathy
- Epilepsy
- Myalgia/Myositis
- Cerebellar Ataxia
- Peripheral Neuropathy
- Brain atrophy
- Irritable bowel syndrome
- Schizophrenia

FACT 7: Where CD/NCGS has affected the gut, taking gluten out of the diet is NOT enough for clinical improvement. The fire of inflammation in the gut must be put out and intestinal permeability MUST be healed to restore absorption. Taking gluten out stops feeding the fire, but the inflammatory cascade has a life of its own and gut permeability continues unless there is a specific healing intervention.

Less than half of patients with coeliac disease on a gluten-free diet have complete normalization of intestinal biopsies, intestinal permeability defects, and antibody levels (after a mean of 9.7 years on a GFD). *Digestive diseases and sciences* April 2010

It is important to understand that children with CD had a 3 fold increase of long-term mortality – WHETHER THEY WERE ON A GLUTEN-FREE DIET OR NOT according to *American Journal of Gastroenterology* April 2007

This suggests taking gluten out of the diet is not enough. Although the villi of CD patients grows back after 1 year on a gluten-free diet, the evidence suggests that increased intestinal permeability and poor absorption – both linked with autoimmunity – is still present. So the gut must be healed and any inflammatory cascade dealt with even after gluten is removed.

"There is a strong activation of immuno-inflammation, both in intestinal biopsy samples and in peripheral blood cells in patients with active CD, with a high chronic release of various cytokines and other molecules with vasoactive properties such as interferon- and interleukins 2, 4, and 10"
The American Journal of Gastroenterology March2003

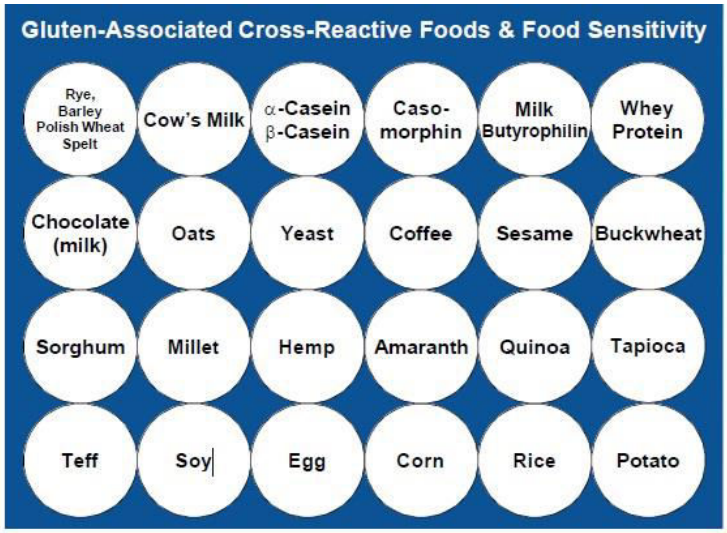
"Gliadin activation of macrophages was found to up-regulate expression of a panel of inflammatory genes and result in the secretion of inflammatory cytokines."
The Journal of Immunology Feb 2006

The difficulty of adhering to a gluten-free diet (GFD) can make prognosis difficult. Strict adherence to a GFD does greatly improve nutritional status but one study found it did not completely normalize 'body composition'. Metabolizing B-vitamins, in particular, may be reduced. Hallert et. al. found that even celiac patients on long-term gluten-free diets with normal gut villi, had reduced plasma B-vitamin (homocysteine) levels. Forty-five percent of celiac disease patients on a gluten free diet for decades had reduced bone mineral density (osteoporosis).

Increased rates of disease' indicate that neurological problems can manifest themselves even when 'overt malabsorption' is not present in some patients. While substantial improvement in gut mucosa and other factors did occur 2-4 years after beginning a gluten-free diet, lactase activity was still reduced. One study suggested 'leaky gut' was still common a year after beginning a gluten-free diet.

Finally, quality of life measures improve after initiating a gluten-free diet but are still somewhat reduced relative to the general population, so simply removing gluten, while beneficial, is often not sufficient to return one to full health.

The Cross-sensitization Factor: Taking gluten out of the diet may not be enough because of the issue of cross-sensitization.



Even minute traces of gliadin or their cross-reactive foods are capable of triggering a state of heightened immunological activity in gluten sensitive people.

Journal of neurology, neurosurgery, and psychiatry. Dec 1997

Cross-sensitization refers to a process where-by a person becomes sensitized to new substances. For instance, in gluten sensitivity, the original sensitivity to proteins called gliadins found in cereals in the Triticum genus (wheat, rye and barley) can lead to further sensitization to other produce.

Foods known to cross react with purified gliadins (wheat proteins) make up the entire first line (rye, barley, spelt, cow's milk, whey protein plus milk chocolate and coffee). The other foods on the chart are commonly eaten on a gluten-free diet where sensitivity may also arise. Some foods such as oats are prepared in facilities where gluten contamination is common. Even small traces of gliadin can trigger an immune response in very gluten sensitive people.

FACT 8: The current test for CD not only misses out on testing for cross-sensitized foods but also ignores the fact that people react to a RANGE of gluten proteins, hence false negatives are prevalent in the standard Celiac test. Also, there are at least 24 celiac-associated auto-antibodies that could be tested for, not just gut related autoantibodies

The Standard coeliac test is made up of three elements:

Two antibodies to parts of the BODY – ie AUTOIMMUNITY in the gut:

1/ To the endomysium – the sheath which encloses the villi

2/ To transglutaminase – an enzyme inside the endomysium

Antibodies to an environmental factor – i.e. ALLERGY to gluten

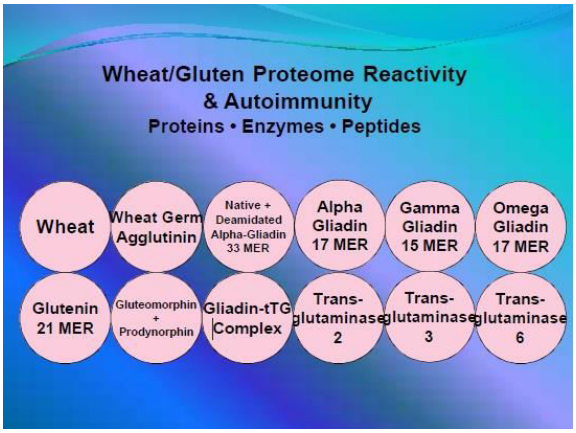
3/ Antibodies to the gluten protein gliadin. Recently this has changed to deamidated gluten which has been found to be more accurate to diagnose CD, but not NCGS.

Problems With The Current Testing Protocols

(1) Antibodies to endomysium and transglutaminase are EXECELLENT markers for TOTAL VILLUS ATROPHY (i.e. celiac disease) but are highly unreliable diagnostic markers for the partial villous atrophy or increased epithelial lymphocytes found in non-celiac gluten sensitivity (NCGS). Only 24% of patients with partial villous atrophy (NCGS) and coeliac disease were diagnosed correctly using antibody tests in two studies.

The antibody test to the gluten protein ONLY checks for one TYPE of gluten (called the 33-mer peptide.) If all you do is check the gluten 33-mer (the standard test) you'll miss gluten sensitivity 50% of the time. Studies consistently show that most people with CD react to a range of gluten peptides, some as strongly as the gluten-33 mer that is typically tested for. Note gluten is found in ALL grains, however a subset of gluten proteins particularly toxic to some humans are found in wheat, rye and so on. An assay that includes IgA and IgG antibodies for a range of gluten peptides is therefore desirable.

"Our present results indicate that CD patients are capable of responding to a large array of gluten peptides. We found that 50% of these patients do not respond to the alpha-GLIA peptide but to a diverse set of gliadin and glutenin peptides, including 6 novel epitopes." *Gastroenterology* June 2002



Prevalence

If we take into account that gluten sensitivity doesn't just cause CD, but also partial villous atrophy and gut inflammation, **AND** probably triggers many disorders outside the gut including autoimmune disorders, **AND** the fact that people react to a range of gluten molecules, not just the one in the standard CD, it begs the question; how much of the population is sensitive to some form of gluten?

I believe it is between 10% and 35% of the population.

"Gluten Sensitivity (GS) is a state of heightened immunological responsiveness to ingested gluten in genetically susceptible people. It represents a spectrum of diverse manifestations, of which, the gluten sensitive enteropathy known as CD is one of many. Adverse reactions to the toxic family of gluten proteins found in wheat, barley, rye, and their derivatives may trigger a heterogeneous set of conditions, including wheat allergy (IgE), NCGS, and CD, that, combined, affect between 10 – 35% of the population."
Celiac Disease and Non-Celiac Gluten Sensitivity: the Evolving Spectrum

FACT 9: The limited research on dietary intervention and CFS is still mainly based on the classical approach to food allergy which is IgE mediated. Despite clear evidence for non-IgE mediated food sensitivities, studies on CFS continue to ignore the research

In the *Scandinavian Journal of Gastroenterology* in Sept 2012 in the paper called "Functional bowel symptoms, fibromyalgia and fatigue: a food-induced triad?" researchers reported:

"In a prospective study, 84 patients referred to our outpatient clinic for investigation of perceived food hypersensitivity were enrolled consecutively…

…Neither IgE-mediated food allergy nor organic pathology could explain the patients' symptoms."

The above paper did not test for CD, or NCGS nor IgG or IgA cross-sensitised foods and reflects what Manu et al concluded back in 1993 below, which is essentially that CFS patients' assertions that self-reported intolerances to food are mental or emotional in origin.

"Intolerance to various foods is reported often by patients seeking evaluation for chronic fatigue…To assess the prevalence and significance of this phenomenon we studied 200 consecutive patients with chronic fatigue who were given a comprehensive medical and psychiatric evaluation...

These data suggest that intolerance to multiple foods is probably not a cause or the effect of chronic fatigue, but rather one of the manifestations of the somatization trait expressed in these patients." *The International journal of eating disorders*. March 1993

The food intolerances in the above study were assessed simply by asking patients which foods they were intolerant to. In classical IgE allergy, foods cause immediate and obvious reactions which can easily be self-identified, unlike Ig**G** reactions where identification of the offending food is much more difficult due to the delayed reaction.

ME/CFS patients may have failed to improve in the studies on the effects of dietary restrictions quoted below because all gluten or cross-sensitised foods were not adequately restricted and there were no specific intervention to heal the gut and reduce inflammation.

"A 24-week randomized intervention study was conducted with 52 individuals diagnosed with CFS. Patients were randomized to either a low sugar, low yeast (LSLY) or healthy eating (HE) dietary interventions…

…In this randomized control trial, a LSLY diet appeared to be no more efficacious on levels of fatigue or QoL compared to HE."

In the 2012 Trabal et. al. study in the Spanish Journal *Nutrición Hospitalaria* the authors took a cross sectional pilot study with 28 patients diagnosed with severe chronic fatigue syndrome and assessed their dietary eating habits with food frequency questionnaires. The reported that 15 patients were restricting gluten and 22 restricted dairy and they found:

"Patients reported different digestive symptoms, which did not improve with the use of exclusion diets," and concluded:

"Dietary restrictions should be based on a proven food allergy or intolerance. Dietary counselling should be based on sound nutritional knowledge."

Despite these negative studies, Logan and Wong reported on several studies where dietary restrictions made a large improvement in ME/CFS patients:

Nisenbaum et. al. presented an abstract at the American Association for Chronic Fatigue Syndrome conference in Seattle in January 2001, showing that 54 percent of a sample of CFS patients had attempted unspecified dietary modifications. Of these individuals who modified their diet, 73 percent reported the dietary changes were beneficial in reducing fatigue.

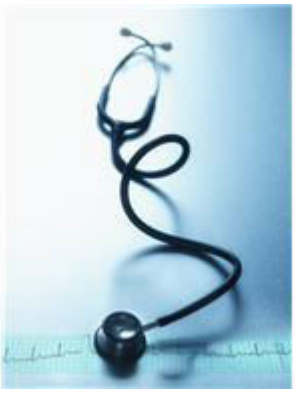
In an Australian study, CFS patients eliminated wheat, milk, benzoates, nitrites, nitrates, and food colorings and other additives from their diet…Of the CFS patients who complied, the results were remarkable: 90 percent reported improvement in the severity of symptoms across multiple body symptoms, with significant reduction in fatigue, recurrent fever, sore throat, muscle pain, headache, joint pain, and cognitive dysfunction. Furthermore, the elimination protocol resulted in a marked improvement in IBS-like symptoms among all patients; a significant finding because CFS patients have a high rate of IBS.

The results of this study support the findings of Borok published in the South African Medical Journal over a decade ago. Borok cited a strong correlation between CFS and the presence of food intolerance. He reported alleviation of chronic fatigue among CFS patients (n=20) after removing certain foods from the diet, with milk, wheat, and corn among the top offenders." *Alternative Medicine Review 2001*

At the moment, no studies have been done testing ME/CFS patients correctly for CD and NCGS, nor have there been studies testing the effectiveness of introducing a strict gluten-free diet and with a gut healing anti-inflammatory intervention.

FACT 10: Every Person With Chronic Fatigue Syndrome Should Be Screened for Coeliac Disease and Non Celiac Gluten Sensitivity as Part of the Differential Diagnosis of the Condition

Many factors suggest CD and NCGS should be part of the differential diagnosis of ME/CFS.



Neurological symptoms are common. Back in 1999, Luostarinen et. al. in *European Neurology,* stated that CD should be considered in all patients presenting with neurological disturbances such as memory deficits and ataxia of unknown etiology.

Small-fibre neuropathy and muscle pain can be induced by gluten sensitivity. Symptoms of small-fibre neuropathy such as tingling, burning pain and tightness, stabbing pain, pins and needles, itchiness and intermittent numbness in different parts of the body, are commonly experienced in ME/CFS. Gluten triggered autoimmune ganglioside antibodies can produce all these symptoms.

Rituximab and other studies suggest autoimmunity is likely to be present in a subgroup of ME/CFS patients. Chronic disorders such CD and NCGS which cause B Lymphocytes activation could trigger autoimmune processes in the body. Some ME/CFS patients could have improved when Rituximab knocked out gluten triggered B lymphocyte activation.

Several studies suggest ME/CFS is an inflammatory disorder. The landmark 2000 *Lancet* study that identified non-IgE mediated food intolerances demonstrated that individuals with non-IgE mediated food intolerance had a significant elevations in inflammatory cytokines (interleukin-4, interferon gamma, TNF-α) when given a dietary challenge of dairy and wheat.

The authors noted that cytokine elevations could account for the post-challenge symptoms experienced such as headache, myalgia, joint pain, and gastrointestinal disturbance – all of which are common in ME/CFS.

"We found that food provocation in food intolerant patients was characterised by a general and systemic immune activation accompanied by an increase in systemic symptoms. Our findings might be important for the understanding of the mechanisms involved in the pathogenesis of food intolerance."
The Lancet July 2000

Other more direct links to coeliac disease and chronic fatigue syndrome exist. Critique of the diagnostic criteria for ME/CFS asked why ruling out CD was not included. Skowera et.al. found a high prevalence of markers of Celiac disease in 100 CFS patients in 2001.

"given our prevalence of 2%, and the fact that there is a treatment for CD, we now suggest that screening for CD should be added to the relatively short list of mandatory investigations in suspected cases of CFS." *Skowera et. al. 2001*

As we have discussed, sensitivity to gluten is likely to be much higher than 2% in the CFS population, as CD is characterized by total villous atrophy and thus misses out the gluten sensitive individuals with partial or no villous atrophy. We've also shown that a missed diagnosis of gluten sensitivity is more dangerous than a diagnosis of Celiac disease since individuals with gluten sensitivity, but not celiac disease, will probably maintain a state of gut inflammation that can trigger neurological, autoimmune and other issues.

This probably also explains why another preliminary paper in the *International journal of clinical practice* in 2001, found no link between CD and Chronic Fatigue Syndrome.

Why You Probably Aren't Getting this Information From Your Doctors

Why is celiac disease so little discussed in the ME/CFS Community? The same reason that many ME/CFS patients are probably not particularly aware of Ehlers Danlos Syndrome or Chiari malformation or many alternative health treatments.

First of all gastroenterologists tend to read Journals directly related to, well to…gastroenterology. They don't have time to read the Journals in Hepatology, Immunology, Pathology or Nutrition, and therefore they are not connecting the dots and miss out on vital information that does in fact relate to their practices from other medical specialities.

Second, Doctors in general have limited time and therefore focus on their specialties, and much doctor education comes from drug company representatives showing them the papers which support their latest drug treatments.

Third, nutrition is not given a high priority in medical school. I have spent 10 years collating and synthesising data on gluten sensitivity. In medical school, doctors are only required to complete just 25 hours of training in nutrition. And:

"Only 28 (27%) of the 105 Medical Schools met the minimum 25 required hours of nutrition education set by the National Academy of Sciences; 6 years earlier, in 2004, 40 (38%) of 104 schools did so." *Academic Medicine*, Vol. 85, No. 9 / September 2010

Finally, some of this information is cutting edge, and cutting-edge information can take decades to filter down from the research field to the standard physician's office. In the 1970s it was estimated the time it took for published research to be applied in clinical practice with patients was about 65 years! With the internet, this has probably more than halved.

In conclusion, it's not your Doctor's fault – she/he is overworked as it is and is dealing with an already very complex disorder. They can't be expected to be on top of everything. Therefore, as we all know, it's best to get educated, take this information to your Doctor if needed and don't wait around for 30 years before your Doctors finally give YOU the information.

I Have Chronic Fatigue Syndrome – What Can I Do To Determine if I have Celiac Disease or Non-Celiac-Gluten Sensitivity?

How Do I Get Tested?

First, have the blood test done for CD. If that comes back negative, check for NCGS first by Array #3 antibody testing from Cyrex Labs. If that's not available, a trial period of eliminating gluten is rational.

If you are having an endoscopy/biopsy done, request that an IEL (Intraepithelial lymphocytes) count be done to assess inflammation in the gut. Most pathologists don't do it but it's easy and inexpensive (about $40). This test will determine if you fall into the inflammatory sub-clinical group of NCGS patients.

If the Array 3 comes back positive, you can then request Array 4 from Cyrex labs to test for cross-sensitized foods. The lab automatically saves the original blood sample for 3 months so another blood sample is not needed.

You may already know you have some form of gluten sensitivity; to confirm this, do the same test as above. Note: don't worry if you have not eaten gluten before doing the test and don't go back on gluten for the test because it can have very adverse effects on some patients. Much of

the time, even if you thought you were gluten-free, you've probably still been exposed, unknowingly and this testing will confirm that.

In the UK and Europe Regenerus Labs offer the Cyrex Labs testing.

How Do I Follow a Gluten-Free Diet?

An important fact is that mortality rates rise after the first year of going gluten-free possibly due to gluten withdrawal and because blood sugar problems arise as some people start to skip meals.

Cardiovascular disease was the most common cause of death in Coeliac disease, followed by malignancy. The highest HRs were seen in the first year after biopsy, with an HR of 3.78 for death due to malignancy and 1.86 for CV death.
Journal of the American Medical Association.

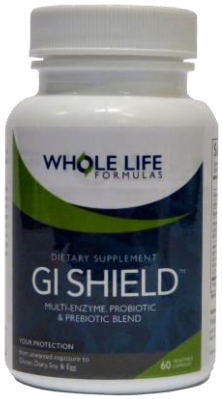
I recommend a "Modified gluten-free" diet, which is essentially a gluten-free diet designed to manage blood sugar imbalances and the crashes which often occur in the early withdrawal phase from gluten. A low sugar diet, meals five time per day and other standard recommendations to manage blood sugar levels are needed to prevent blood sugar falling too low or rising too quickly leading to crashes.

Following a gluten-free diet where even that crouton in your salad can cause problems takes time to master. Did you know gluten is present in cosmetics and personal hygiene products too? The gluten doesn't generally go through your skin (unless it has been through nano-technology), instead it gets *inhaled* with similar adverse effects as oral consumption.

For more details of my products and further support on moving to a gluten-free diet see www.TheDr.com

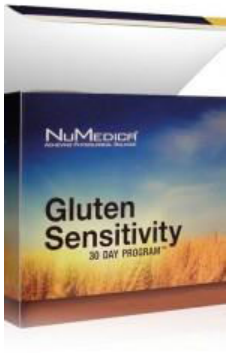
theDr.com

Your Resource for Gluten Sensitivity, Celiac Disease, and Autoimmune Education, As Well As Lab Testing and Interpretation, Nutrition Consultations and Products to Support You on Your Path to Wellness.



GI Shield™ is protein busting formula uniquely designed with powerful enzymes, prebiotics and probiotics to break down gluten, dairy, soy and egg proteins within 90 minutes by targeting both internal and external peptide bonds.* GI Shield™ goes beyond the traditional DPPIV enzyme, offering superior degradation of these proteins by breaking down unhydrolyzed peptides.* Additionally, the highly specialized prebiotic, PreForPro™ is unique in supporting the proliferation of beneficial bacteria in both the small and large intestines.* GI Shield was developed by Dr. Tom O'Bryan, international recognized speaker and expert.

Lab Tests theDr.com is your resource for information about gluten-related disorders. Learn how more than 300+ symptoms from them may be the result of a wide variety of health issues, including autoimmune diseases. We offer both test interpretation and nutrition consultations. Please note that test interpretation consultations DO NOT include personalized recommendations. Please visit our Consultation Page for details.



Gluten Sensitivity Support Kit formulas work with a Gluten-Free diet to minimize the negative effects of gluten exposure in individuals with Gluten Sensitivity issues. Gluten Sensitivity Program™ is a kit composed of nine formulas chosen for their ability to support the repair of damaged tissue, to restore immune system and eicosanoid balance and revitalize overall health in gluten sensitive individuals.* Also included is an informative program guide offering guidelines for living a healthy, gluten-free lifestyle.*

theDr.com, Towards Healing the Planet, One Person At A Time

*These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.