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The Confusing Landscape of Wheat Hypersensitivities:

Making the correct diagnosis & management

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Objectives

Upon completion of this learning activity, participants should be able to:

- Recognize wheat-related disorders.
- Evaluate patients whose symptoms are related to consumption of wheat (& similar grains).
- Diagnose and prescribe personalized management for patients with wheat-related disorders.

Wheat *(Triticum aestivum)* Proteins

A. Water-soluble albumins
B. Saline-soluble globulins
C. Water-insoluble proteins:
   - Alcohol-soluble prolamins, including monomeric gliadins (α/β, γ , and ω)
   - Alcohol-insoluble polymeric glutenins

Gluten is 80% of the wheat proteins; of 2 main components: gliadins & glutenins.

Additional (gluten-like) proteins similar to wheat prolamins:

- hordein in barley
- secalin in rye
- avenin in oats

Disorders Related to Consuming Wheat (& similar grains)

I. Wheat allergy (WA)

II. Celiac disease (CD)

III. Non-celiac gluten/wheat sensitivity (NCGS/NCWS)

IV. "*Gluten madness*"!

I. WHEAT ALLERGY

- Wheat is the most common allergenic cereal grain.
- Prevalence <0.5%:
  - typical IgE-mediated reactions (GI, skin, resp, Anx). Most commonly seen in children & usually resolve in a few years.
  - baker's asthma; by inhalation, not ingestion; related to α-amylase inhibitor
  - post-prandial wheat-dependent exercise-induced anaphylaxis (WDEIA) within 2-4 hr; related to ω-5 gliadin.

Food-dependent, exercise-induced anaphylaxis (Post-prandial exercise-induced anaphylaxis)

- A distinct form of allergy in which anaphylaxis occurs only when the patient exercises within “2 hr” of eating the food.
- The onset of Sx can be delayed for several hours.
- Its precise mechanism remains unclear.
- Can be caused by any food or multiple foods, individually or only in combination.
- Wheat protein ω-5 gliadin (Tri a 19) is the most common.

Delayed Food-Dependent Exercise-Induced Anaphylaxis

(Oyefara & Bahna Allergy Asthma Proc 2007;28:64)

- A 16-y-o with recurrent WDEIA since 11 yr of age.
- 1 hr after eating a sandwich, he played basket ball for 1 hr.
- 5 hr later, while alone at home, had generalized itching & SOB.
- Immediately called 911 but lost consciousness before talking or reaching his epi autoinjector.
- Paramedics broke the door & resuscitated him.
- Delayed FDEIA is unpredictable & can be life-threatening, it would be prudent to delay exercise for ≥ 6 hr.

Diagnosis & Management of Wheat Allergy

Diagnosis:

Symptoms, SPT/sIgE, elimination-challenge test.

Management:

- Wheat elimination; may tolerate other cereal grains.
- Symptomatic treatment for accidental exposure.
- Periodical challenge to test development of tolerance.
- Prognosis is generally good; most resolve in few years except WDEIA.
- Potential immunotherapy.

II. CELIAC DISEASE

- An autoimmune small bowl disorder occurring in genetically susceptible individuals causing chronic malabsorption.
- Linked to grain prolamins:
  - *Gluten* in wheat ++++
  - *Secalin* in rye +++
  - *Hordein* in barley ++
  - *Avenin* in oat +
- The offending quantity & symptoms' severity vary; usually worse in children.

CD Epidemiology

- Rare prevalence:
  - - globally 1.4% by serologic testing & 0.7% by biopsy.
  - - highest in northern Europe (1 in 300)
  - - low in US (1 in 5,000-10,000)
  - - very rare in Chinese, Japanese & Sub-Saharan Africans
- F > M ; 2:1
- Age of onset is mostly within months of introducing gluten but varies (even among siblings). May be delayed till late childhood or adulthood.

Is there a Role for IgE or IgD in Celiac Disease?

(Bahna, Tateno & Heiner: Ann Allergy 1980; 44:146)

Sera of 17 patients with gluten-induced celiac disease were studied. Total serum IgE and IgD, as well as specific IgE and IgD antibodies to selected food antigens, were determined. Total IgE levels were within the normal range. Specific IgE antibodies to wheat, alpha-gliadin, cow's milk, rice and buckwheat were comparable to those of normal controls. In the celiac subjects total IgD levels were also within the normal range but IgD antibodies to wheat were high whereas IgD antibodies to milk were lower than in pooled normal sera. The levels of IgE or IgD antibodies to either wheat or milk showed no relationship to the presence of precipitins to the antigens of these two foods. The study did not demonstrate a role for IgE in celiac disease. That IgD antibodies may play a role is suggested by the elevated serum IgD antibodies to wheat antigens.

6th International Symposium on Immunological & Clinical Problems of Food Allergy, Lugano, Switzerland, September 24-26, 1995.

A debate: Is Celiac Disease Allergy?

Wüthrich B, Ortolani C (eds): Highlights in Food Allergy.
Monogr Allergy. Basel, Karger, 1996, vol 32, pp 204–210

Coeliac Disease: A Food Allergy?

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Wüthrich B, Ortolani C (eds): Highlights in Food Allergy.
Monogr Allergy. Basel, Karger, 1996, vol 32, pp 211–215

Celiac Disease: A Food Allergy? Contra!

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Celiac Disease Pathology

- Biopsy: intestinal villous atrophy, crypt hyperplasia & intra-epithelial lymphocytic inflammation. Increased interleukin-15 involved in intestinal mucosal damage.
- Serology: IgA anti-endomysium & anti-transglutaminase in > 95%.
- Genetics: HLA haplotypes DQ2 &/or DQ8 in 99% of patients vs 40% in the gen population; i.e., not every genetically-predisposed person develops clinical CD.

Clinical Manifestations of Celiac Disease

(in alphabetical order; None pathognomonic!)

Classic symptoms	Nonclassic symptoms
Abdominal distension	Arthritis
Anorexia	Aphthous stomatitis
Chronic or recurrent diarrhea	Dental enamel defects
Failure to thrive or weight loss	Dermatitis herpetiformis
Irritability	Iron-deficiency anemia
Muscle wasting	Short stature

Co-morbidities of Celiac Disease

Autoimmune Disorders	Genetic Syndromes	Other Conditions
Type-1 diabetes (4-8%) Thyroiditis (4%) Arthritis (1.5-7%) 1ry biliary cirrhosis (6%)	Down synd (5-12%) Turner synd (4-8%) Williams synd (8%)	IgA deficiency (2-8%) Neurologic/psychologic: - Ataxia - Depression - Epilepsy with intra-cranial calcifications IgA nephropathy Low bone density

Dermatitis Herpetiformis

(Not to be confused with dermatitis herpeticum (H simplex on AD)

In 15-25% of celiac disease.

- Very pruritic red purplish papular/vesicular lesions.
- While lesions heal, new appear. Leave purple marks for weeks or months.
- More on larger body parts (buttocks, back, abdomen, legs, arms)
- Biopsy immunofluorescence: typical granular IgA deposits in the dermo-epidermal junction.
- Many dermatitis herpetiformis patients don't have GI Sx, yet 90% have some degree of intestinal damage.

Diagnostic tests for celiac disease

- Serology
- HLA typing
- Biopsy
- Gluten elimination/challenge

Serologic tests for CD

Antibody test	Sensitivity %	Specificity %
IgA endomysium Ab (IgA EMA)	85 - 98	97 - 100
IgA tissue transglutaminase Ab (IgA tTGA)	90 - 98	95 - 97
IgA deamidated gliadin peptide Ab (IgA DGP)	94	99
IgG deamidated gliadin peptide Ab (IgG DGP)	92	100

- IgA EMA & IgA tTG tests have the highest diagnostic accuracy.
- IgA & IgG antigliadin tests have low diagnostic reliability, with frequent false positivity.
- IgG DGP is best in IgA-deficient subjects.
- All 4 Abs levels fall with treatment & can be used for monitoring compliance with GFD.

HLA testing in CD

- Testing for HLA DQ2 & DQ8 haplotypes has 95% sensitivity, but 30% specificity, i.e., very high negative predictive value.
- HLA testing is useful in the following situations:
  - Seronegative patients with equivocal biopsy findings
  - Patients who are already on GFD without prior biopsy or serology testing.
  - Patients with equivocal serology & histology
  - Patients with IgA deficiency and equivocal biopsy or IgG DGP Ab

Biopsy for Celiac Disease

- Diagnosis of CD usually requires confirmation with duodenum biopsies (1-2 from bulb & 4 from distal duodenum).

- Exceptions: (biopsy not necessary)
  - children with high IgA anti-tTG (>10× upper limit of normal) with a positive IgA anti-EMA.
  - patients with positive serology & a biopsy-proven DH.
  - first-degree relatives with typical symptoms, positive serology, HLA DQ2/DQ8 & definite improvement on GFD.

Is gluten challenge needed?

Challenge followed by serology & biopsy is needed in:

- Subjects who are already on GFD without prior serology testing or biopsy.
- Patients on GFD with positive serology but normal or equivocal biopsy.

Dose: usually at least 2 slices of bread per day (3 g gluten)

- Sx within a few days
- Serology in 4 wk
- Biopsy 4-8 wk

Management of CD

- Avoid wheat, barley, rye (& ? oat) for life.
- Ingesting 50 mg gluten/day can cause intestinal damage for CD pts.
- According to FDA, a product can be labeled "*Gluten-free*" if its gluten content ≤20 ppm. (This means that symptoms may occur after eating ≥5 pounds of gluten-free food!!!)
- Monitor compliance with GFD (IgG anti-gliadin); the degree of strictness may vary among patients.
- Monitoring for autoimmune diseases, diabetes & lymphoma.

Potential future therapies for CD

(D'heedene, Vanuytsel, Wauters: Clin Nutr 2024;43:1240)

Future studies will likely focus on the use of supplemental drugs in conjunction to GFD to protect against accidental ingestion of small quantities of gluten.

- developing an antibody against IL-15.
- developing a vaccine aims at re-programming T-cells that trigger the inflammatory response to gluten.
- recombinant proteases gluten-specific given orally to protect against gluten-induced mucosal injury.

III. NON-CELIAC GLUTEN/WHEAT SENSITIVITY

Also called:

Non-celiac gluten intolerance
Non-celiac wheat intolerance
Non-celiac wheat sensitivity
Non-celiac disease, non-wheat allergy gluten sensitivity

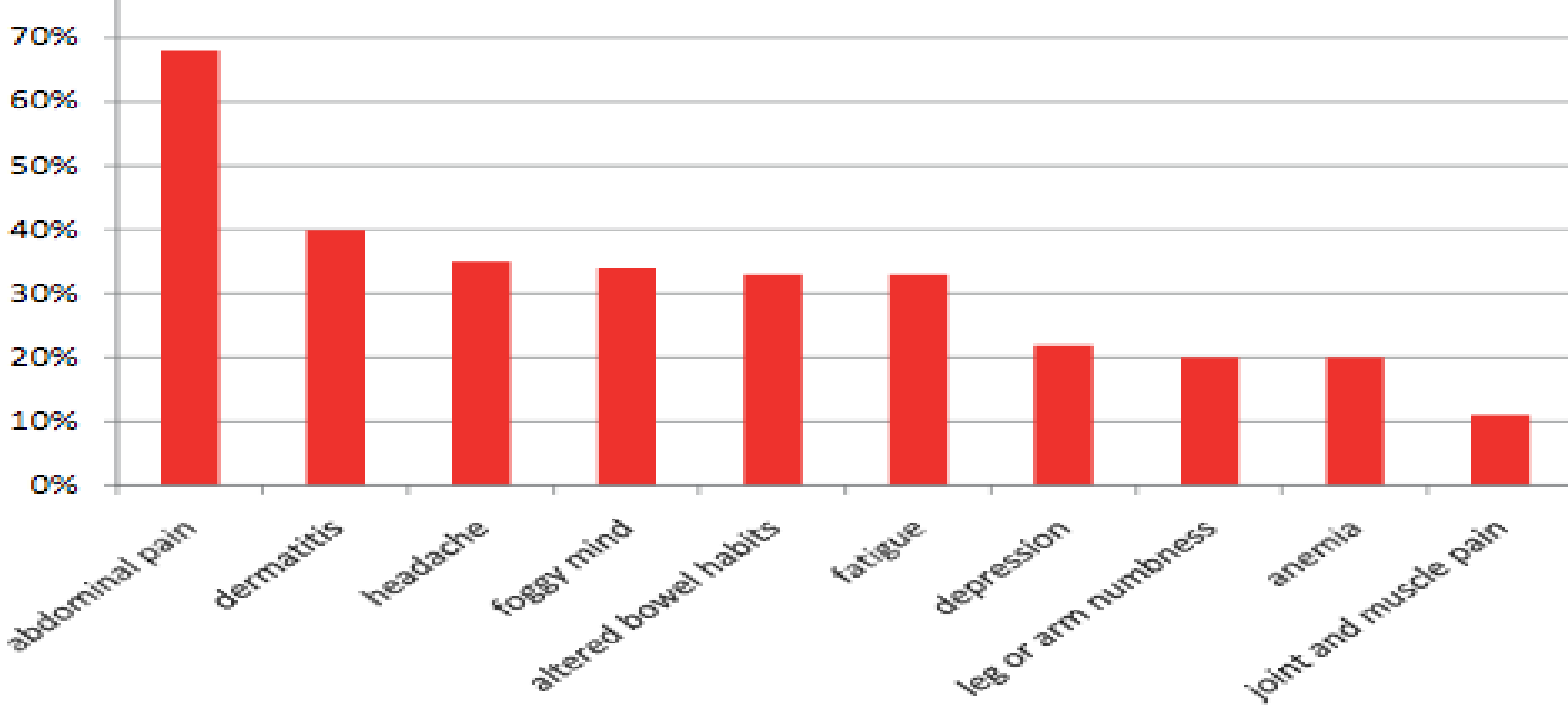
Interest in this area began in 1980s and is constantly increasing.

Remained controversial but has been recognized as a clinical entity in 2012,

Non-Celiac Gluten (Wheat) Sensitivity (NCGS)

(Zopf & Dieterich: Dtsch Med Wochenschr 2015;140:1683)
(Piotin & de Blay: Clin Rev Allergy Immunol 2025;68:94)

- Self-reported, various heterogenous Sx occurring hours to days after gluten/wheat consumption.
- Subjects neither have CD nor WA, yet have Sx that improve on GFD.
- Pathogenesis is not well understood. Small intestinal biopsy is typically normal or show mild non-specific inflammation or inconsistent cytokine dysregulation.
- Lacks serologic biomarkers.
- Among proposed mechanisms is the neuro-immune or gut-brain axis and the role of microbiota.



Symptoms reported by subjects with non-celiac gluten sensitivity (NCGS)

(Rathi & Zanwar: J Assoc Physicians India 64:46, 2016)

[According to data from: Sapone et al. BMC Med 2012; 10:13, and .Volta et al. J Clin Gastroenterol 2012;46:680]

NCGS Diagnosis

(Cárdenas-Torres et al: Medicina (Kuanas) 2021)

- Primarily self-diagnosed (claimed); based on subjective heterogenous Sx that appear after hours or days of gluten (wheat) intake.
- No objective criteria or biomarkers.
- Placebo-controlled blind challenges are difficult to perform & assess.
- A meta-analysis [Lionetti et al: Front Physiol 2017; 8:621] evaluated 11 studies that carried out DBPC challenges noted marked differences in:
  - amount of gluten used & amount tolerated
  - type of placebo
  - duration of the gluten intake
  - washout period between challenge & placebo

NCGS Diagnosis *(Salerno Experts' Criteria)*

(Catassi et al 2015, Khan et al 2020)

"***Salerno Experts' Criteria***" (meeting in Salerno, Italy; 6-7 Oct 2014)

- Improvement after GFD for 6 wk.
- DBPCC with gluten (8 g/day) & placebo each for 1-wk with 1-wk washout of strict GFD . Using a self-administered scale, 30% difference in Sx score would be diagnostic of NCGS.

.Limitations:

- Experts opinion without objective criteria of improvement; the 30% difference is arbitrary.
- Time-consuming requiring multiple elimination-challenge phases.
- Requires high patient's adherence.
- Focus on gluten; miss NCWS cases caused by other wheat components.
- Potential misdiagnosis of other diseases causing the Sx.

NCGS Epidemiology

(Piotin & de Blay: Clin Rev Allergy Immunol 2025;68:94)

- Sx are hard to reproduce even with some double-blind challenges ; only one-third of patients identified gluten correctly (Zanini et al 2015, Molina-Infante & Corroccio 2017).
- High placebo & nocebo rates, reflecting a strong psychologic role & expectancy (de Grafff et al 2024, Hindson 2024).
- Exact prevalence is unknown; estimates <1% to up to 15%.
- More reported by young adults (3rd & 4th decades); F>>M (5:1), more in urban.
- The observation that some patients reported Sx to wheat but not to gluten, suggests that other components of wheat may be responsible. Hence, the preference of NCWS over NCGS:
  - alpha-amylase/trypsin inhibitors (ATIs) - protein
  - fermentable oligosaccharides disaccharides, monosaccharides & polyols (FODMAPs) – carbohydrate
  - wheat germ agglutinin (WGA) – lectin

NCWS Management

- Basically GFD – the degree of which may vary from one patient to another; Shared-Decision-Management.
- Dietitian involvement to guard against malnutrition (Vici et al 2016, Potter et al 2018, Skodje et al 2019); GFD often:
  - lacks iron, folate, niacin, riboflavin & thiamin.
  - increased sugar, salt & fat.
- Management of stress resulting from following GFD (deprivation & cost) or from dismissing the Dx without identifying an alternative underlying disorder.

IV. "*GLUTEN MADNESS*" *[S Bahna]*

Exponentially increasing claims of gluten-related symptoms!

- Non-specific symptoms, mostly unheard of!!
- Popularity of claiming gluten-related Sx.
- "*Gluten*" is a media's popular hype topic.
- Attractive magazines packed with GFD articles & advertisements.
- The multi-million GFD industry.

The Influence of Internet & Media

Obesity, GI & Gyn disorders claimed to gluten (a)

-"Turn off those fat-burning genes by eating the right foods, like eggs, resveratrol-rich red fruit, and gluten-free grains."
-"To regain all the vitality-boosting energy, going gluten-free can help."
-"Wheat is a source of gastric distress for many, even those who don't suffer from celiac disease."
-"Emulsifiers are often made from gluten and have been associated with an increased risk of colitis."
-" …. gluten may be the trigger for leaky gut syndrome ….. which can allow bacteria and food particles to leak into your abdominal cavity … cause nasty symptoms from bloating and belly pain to more serious issues like peritonitis and even death."
-"For endometriosis sufferers, going gluten-free can make a huge difference."
-"Infertility that has no obvious cause could be the result of undiagnosed celiace."

Neuropsychiatric disorders claimed to gluten (b)

-"If you suffer from regular headaches, going gluten-free might be the answer."

-"Research suggests that gluten sensitivity and sleeplessness go hand-in-hand."

-"Studies have shown that gluten is linked to a wide variety of cognitive disorders."

-"Consumption of wheat and gluten can contribute to wide range of behavioral problems."

-"If you're depressed, cutting out gluten may help alleviate some of your symptoms."

-"Gluten-free diets may alleviate some of the symptoms associated with anxiety."

-"Certain neuropathy sufferers have found that their disease is related to their consumption of gluten."

-"*Many Alzheimer patients may have a previously undiagnosed gluten sensitivity."*

Autoimmune disorders claimed to gluten (c)

-"Dropping gluten from your diet could be the answer to reducing your risk of autoimmune issues."

-"Limit dairy and gluten have been shown to improve thyroid function."

-"Research suggests that gluten-free diets can not only delay, but prevent the onset of diabetes."

-"Gluten is significantly associated with inflammation of the small intestine."

-"Gluten-free helped clear a variety of skin conditions."

-"Eliminating gluten from your diet can improve your cardiovascular function."

-When your body isn't working to fend off inflammatory substances, including gluten, its defenses against germs and disease are heightened."

-"Wheat may spur the development of cancer."

The madness continues

- *"Going gluten-free can make you feel better from head to toe."*
- *"Try cutting it out of your diet for a few weeks; you might be surprised by how much better you feel."*
- *"Cutting out gluten can help both your pet and yourself."*
- *"Celebrities proclaiming GFD has helped them."*

In Conclusion,

Wheat-related disorders are great opportunity for allergists.

YOU are well-qualified to evaluate & treat:

I. Wheat allergy
II. Celiac disease (most cases)
III. Non-celiac, non-allergy, gluten/wheat sensitivities